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HAEMATOLOGY

Based on Dr. Dilip MMS

Part II

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Medicine Made Simple

HAEMATOLOGY
notes

We hope you enjoy using these notes

They have been hand-crafted with an obsessive attention to details, with aim of capturing the course's content in a way that's right for you.

Thank You

Inspired by
Samuel Suresh

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Histiocytic and Dendritic cell disorders

HISTIOCYTIC (vs) DENDRITIC CELLS :

Histiocytes

① Activated macrophages (in tissues)

② CD 68 +

③ Origin – Myeloid lineage (may be CD 11c +)

④ Disorders –

① HLH (Haemophagocytic Lymphocytic Histiocytosis)

② RDD (Rosai - Dorfman Dis.) (Sinus Histiocytosis c̄ massive Lymphadenopathy)

Dendritic Cells

① Antigen Presenting Cells

② Origin –

- Myeloid (CD 11c +)
  - Stratified epithelium (skin / mucus memb.) → Langerhans cell → CD1a +
    - EM – Birbeck granules ('Tennis racket' app.)
    - Disorders – Langerhans cell Histiocytosis (LCH)
  - Tissues except Stratified epith. → Interstitial Dendritic cell
  - Circulation → DC-1 (MDC)
  - → CD 1a –
    - ① Juvenile Xanthogranuloma
    - ② Erdheim Chester Disease
- Lymphoid (CD 11c -) → Plasmacytoid DC (PDC) (resemble Plasma cells)
  - → Produce type I IFN (IFNα) (Storehouse of IFN / IFN producing cells - IPC)
  - → Present in Circulation
  - → a/w SLE

– Key cell involved in SLE → PDC
– Key molecule " " " → } IFN α
– Genetic / Molecular Signature of SLE →

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Haemophagocytic Lymphocytic Histiocytosis :

→ Histiocytes phagocytose other cells of Bone marrow (eg: RBC, Platelets, etc) leading to Cytopenia / Pancytopenia

Pathophysiology → ↑↑↑ Histiocytes [⊕ NK cells / CD8↑]

↓

IL-6 / IL-10 / IL-12 / Soluble IL2 Receptor / IFN γ **

Etiology :

- **Inherited** (Child <3 yrs)
  - **Familial**
    - ↓ Genes (for secretion of Perforins / Granzymes)
      - ↓
      - ① PRF-1
      - ② UNC13D
      - ③ STX 11
      - ④ STX BP2
  - **Immune deficiency**
    - ↓
    - ① Griscelli syndrome
    - ② Chediak Higashi Synd.
    - ③ CD 27 deficiency
    - ④ X MEN syndrome
    - ⑤ Hemansky Pudlak Synd.
- (m/c) **Acquired** (adults)
  - ↓
  - ① **Infections :**
    - a) Viral [HHV-8 / HIV / CMV / EBV]
    - b) Bacterial [TB / Leishmania / Enteric]
    - c) Malaria
  - ② **Auto immune :**
    - a) Macrophage Activation Syndrome (MAS)
  - ③ **Malignant** — Leukemias / Lymphomas

Criteria (for diagnosis) :

- **Clinical**
  - ↓
  - ① Fever (>7d)
  - ② Splenomegaly
- **Laboratory**
  - ↓
  - ① Cytopenias (≥ 2 lineages inv.)
  - ② ↑ Triglycerides (≥ 265)
  - ③ ↓ Fibrinogen
  - ④ ↑↑ Ferritin (>500)
  - ⑤ ↓↓ NK cell activity
  - ⑥ ↑↑ Soluble IL2 Receptor [CD25]
- **Histological**
  - ↓
  - ① Hemophagocytosis (To be shown in Biopsy of BM that 1 cell is engulfing the other cells)

$\boxed{\geq 5/8}$ → Δ- HLH

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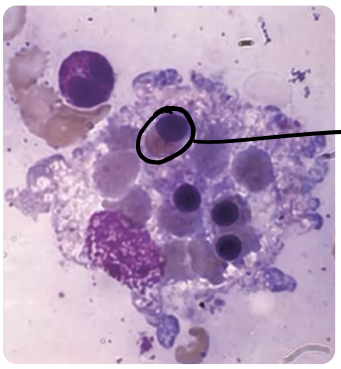

→ BM Biopsy

→ Histiocyte engulfing other cells

Rx: Rx of 2° cause

± Steroids + Etoposide (DEXA) → [HLH 94 protocol] (preferred) / → HLH 2004 Protocol

± Cyclosporine

± Others → Rituximab (CD20-)
Alemtuzumab (CD52-)
Emapalumab (IFNγ-)

ROSAI-DORFMAN DISEASE (RDD):

→ Sinus Histiocytosis & massive Lymphadenopathy

→ Massive Cervical Lymphadenopathy

Biopsy – Histiocytes ↑↑↑ (c̄ in Sinuses) [Non-malignant Proliferation of Histiocytes]

IHC – CD68 +
S-100 +
CD 1a –

Rx – Steroids ± Clofarabine (for Bone/Orbit lesions)

Other features – ↑ Total Count / ↑ ESR / ↑ γ Globulin / Anemia

LANGERHANS CELL HISTIOCYTOSIS:

→ Clonal (Malignant) proliferation of Langerhans Cells

→ Infant / Child ⟹ Skin (Eczema)
↓
not responding to Rx
↓
Biopsy ⟹ [CD1a +] cells

} ± Bone cells (Punched Lytic lesions)

Pathophysiology – BRAF [V600E] (mutation) ⟶ ↑ Severity

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LCH

- **Single System**
  - Unifocal
  - Multifocal
  - No fever / wt. loss
- **Multi System**
  - Low risk
  - High risk → ① Bone marrow ② Liver ③ Spleen (involved) [Poor prognosis]
  - fever / wt. loss

Systems Involved :

① **Bone** → (m/c system involved) → 80%

→ Lytic lesions (Presentation → Asymptomatic / Local pain & tenderness / Soft tissue swelling

→ Site – Child – Skull
Adults – Jaw > Skull
→ Others – femur / Humerus / Ribs / Vertebrae

② **Skin** : [2nd m.c] (most important in children)

- Infants → Brown purplish papules [Hashimoto Pritzker Syndrome / Self-Healing Reticulocytosis]
- Child / Adults → Eczema

→ Often confused for Seborrheic Dermatitis

Other features → Gingivitis, Mucosal ulceration, Intraoral mass } not so important

③ **Lymph nodes** – 20%

→ Cervical LN involved [soft / matted consistency]

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④ Hepatosplenomegaly — Liver, Spleen } High risk ± 1° Sclerosing Cholangitis (PSC)

⑤ Lung — [10%]
- seen more commonly in Smokers
- Pulmonary LCH [ILD]

⑥ CNS — m/c endocrinal disorder
↓
Diabetes Insipidus
± Proptosis

⑦ GIT — [least common]
- diarrhoea ; malabsorption

Older Classification : [Not used now] :

Letterer Siewe Syndrome
↓
- age < 2 yrs
- Multisystemic
- High risk organs like liver, spleen, skin involved
- Lytic lesions in skull

⇓

Other name — Acute Disseminated LCH

Modern class — Multisystem LCH c̄ high risk organ involvement

Hand - Schuller Christian Disease
↓
- Children
- DI

Lytic (skull) — Exophthalmos

- Other name — Multifocal Eosinophilic Granuloma
- Modern — Multisystem LCH c̄ low risk

[Better prognosis because no high risk organs involved]

Eosinophilic Granuloma
↓
- (misnomer) because LCH is d/t Dendritic cells & not Eosinophils
- Adults
- m/c → Bone (Skull)
- Indolent course
- Single system + Unifocal lesion
- Eosinophils appear to ↑ in Bx
- Pulm. LCH [ILD]
  ↓
  Upper lobe / Single lesion / Smokers [Single system / unifocal]

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Rx – ① Single system – ① Resection + radiotherapy
± Topical steroids / PUVA [if skin is involved]

② Multi system – Chemotherapy – ① Vinblastine
② Methotrexate
③ Steroids
④ 6-Mercaptopurine
} might be needed

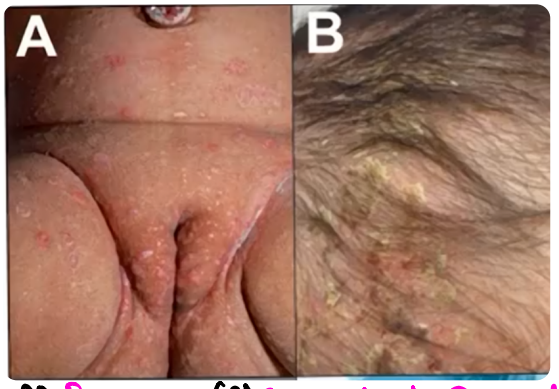
Diagnosis:

① Biopsy → Langerhans cells (tumor cells) + Eosinophils + Histiocytes
[Heterogenous collection of cells]

Nucleus – 'Twisted tower' / 'Coffee bean' shaped

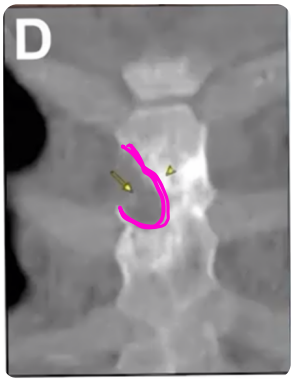
IHC – CD1a +
S100 +
CD 207 + (Langerin)

② Electron Microscopy: 'Birbeck Granules'

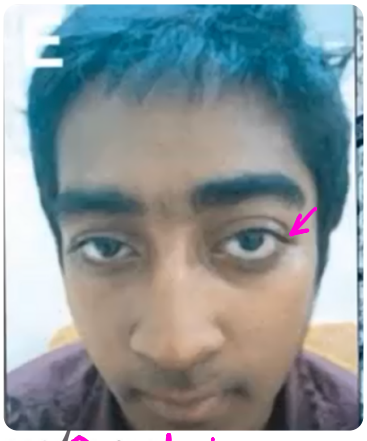


(A) Eczema (B) Seborrheic Dermatitis

Lytic lesion (skull)



Lytic lesion of Vertebral column



Proptosis

Birbeck granules (EM of LC)

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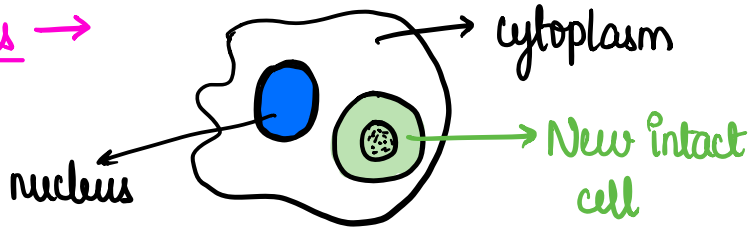
	LCH	RDD
① Etiology	–	–
② a/w HHV 6	+	+
③ Clinical		
a) Skeletal	80%	<10% (rare)
b) LN	20%	>90%
④ Extra nodal	common	uncommon
⑤ Tumor cell	Langerhans cell (L.C)	Non-Langerhans Cell (Histiocytes) – True histiocytic disorder
⑥ Eosinophils	++	–
⑦ IHC	CD1a + / S 100 +	CD1a – / S100 –
⑧ Emperipolesis	–	+++ (Characteristic)

Emperipolesis →



⇒ Cell swallowed is intact & not killed (while in HLH it is killed)

Seen in – RDD
AIH (Autoimmune Hepatitis)
MDS
MPN
Lymphomas / Leukemias

① Megakaryocytes engulfing Hematopoietic cells } ⇒ lymphomas, leukemias, MDS, MPN

② Histiocyte engulfing inflammatory cells → RDD

Juvenile Xantho Granuloma	Erdheim Chester Disease
① < 2 yrs ② Solitary skin lesions (Yellow coloured) ③ m/c – Head/Neck > Upper trunk ④ Bx – Foamy histiocytes (giving yellow colour)	① Multisystem involved ② Xanthogranulomatic lesions seen in – Skin Bone → Osteosclerotic lesions Orbit Retro orbital [Multiple myeloma – Osteolytic lesions POEMS syndrome – Osteosclerotic lesions]

Cellular Mechanisms of Innate Immunity

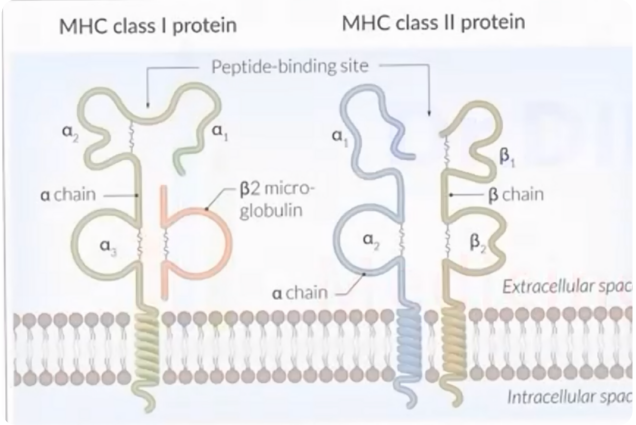
MHC PROTEINS :

→ Cellular mechanisms are responsible for :

① Respiratory Burst.

② HLA - MHC
gene → Protein

[HLA gene - Chr 6]

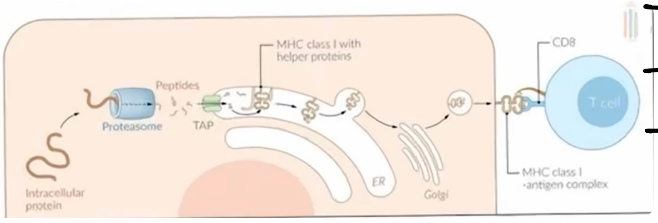


Types :

	MHC - I	MHC - II
① Genes	HLA A/B/C	HLA DR/DQ/DP
② Chains	3α [$\alpha_1 \alpha_2 \alpha_3$] 1 β	2α [α_1, α_2] 2β [β_1, β_2]
③ Peptide Binding site	b/w α_1 & α_2	b/w α_1 & β_1
④ T-Cell Binding	CD 8	CD 4
⑤ Binding site of T-cell	Binds to α_3	binds to β_2

Mechanism of Antigen Presentation :

① MHC - Class I :



→ Endogenous / Intracellular Ag [Virus/tumor]
→ Processed by Proteosome
→ Ag enters the Endoplasmic Reticulum through TAP

→ Certain Dendritic cells process some exogenous Ag & present through MHC I
→ All nucleated cells have MHC I
→ Virus (HIV) & Tumors ⟹ ↓ MHC I
→ Nef Protein in HIV downregulates MHC I & escapes it.

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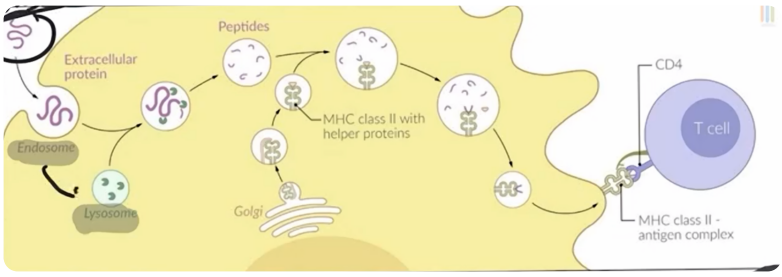
→ NK cell also recognises MHC II & any cell without MHC II are also recognised by NK cell & such cells are killed.

② MHC Class II :



→ usually exogenous Ag are presented
→ Antigen Presenting Cell combines C/ Presents to activated T lymphocyte
→ Endogenous antigens present in Golgi bodies can bind to MHC (β, α sites of MHC II)
⇓
prevented by Invariant chain of MHC II
⇓
'CLIP'

* When Endosome-lysosome compound is formed, Cathepsin L dissolves this CLIP & exogenous Ag now binds to MHC II

Size of Peptide Binding site ⇒ ① MHC I → 8-10 Aa
② MHC II → 13-18 Aa

PATTERN RECOGNITION RECEPTORS :

Types –
① Toll like Receptors
② C-Lectin Receptors
③ Rig-like Receptors
④ Nod like Receptors
} usually are auto-inflammatory

① TLR (Toll Like Receptors) :

Sites – ① Plasma membrane
② Endosome

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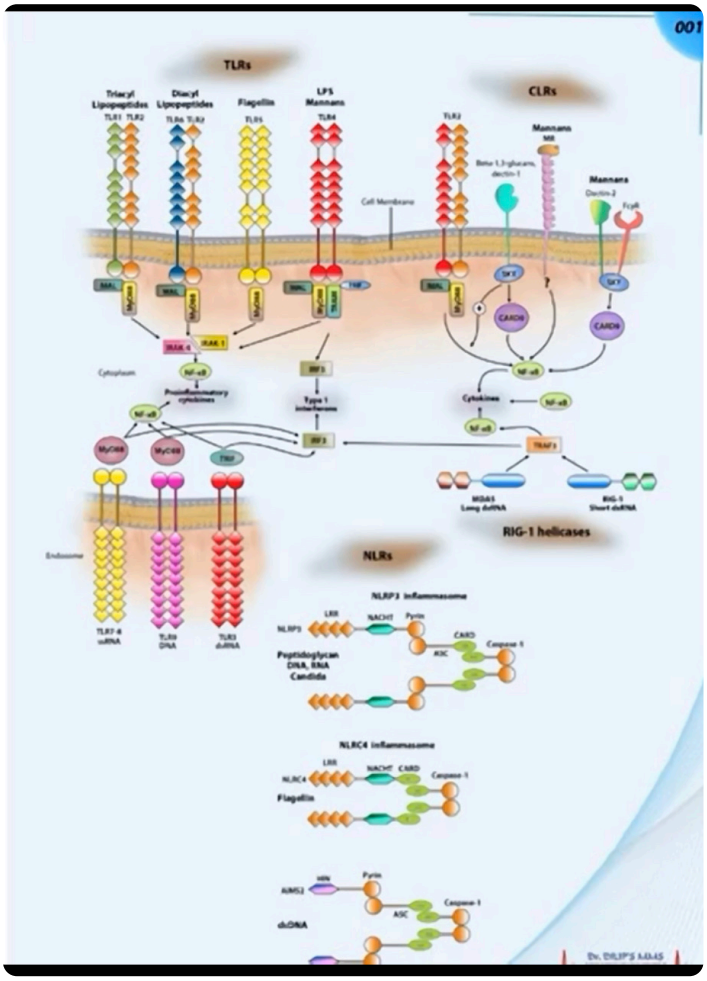
Types – Plasma Membrane – TLR 1/2/4/5/6
Endosome – TLR 3/7/8/9

Ligands –



Plasma Membrane:

1. Triacyl Lipopeptides – TLR 1 & 2
2. Diacyl Lipopeptides – TLR 6 & 2
3. Flagellin – TLR 5
4. LPS Mannan – TLR 4

→ Bacterial Components → they are sensed by TLR 1/2/4/5/6. So, they are present outside the cell, on the Plasma membrane.

Endosome:

1. ssRNA – TLR 7/8
2. DNA – TLR 9
3. ds RNA – TLR 3

→ Viral components → they are sensed by TLR 3/7/8/9. So, they are present inside the cell.

② C-Lectin Receptors:

→ recognise Fungal Components (m/c)

Ligands – ① Mannan
② Dectin

③ Rig-Like Receptors:

→ Rig-1 helicases

Types – recognise

① MDA 5 – long dsRNA
② Rig 1 – short ds RNA

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④ Nod-like Receptors :

Types – ① NLRP 3
② NLRC 4
③ AIMS 2

Ligands :
① Peptidoglycan, DNA / RNA, Candida ⟹ NLRP 3
② Flagellin → NLRC 4
③ ds DNA → AIMS 2

* NLR form
↓
Inflammosome Pathway

⇒ TLR, CLR, RLR, NLR ⟹ Pathology associated Molecular Pattern (PAMP) / Damage associated Molecular Pattern (DAMP)

① High Mobility Group Box-1 [TLR 2/4]
② Uric acid [NLRP 3]

* End result of TLR & CLR pathways ⟹ ↑ NF kB, ↑ ILR 3

[Intracellular receptors – ↑ both (ILR 3 > NF kB)
Extracellular receptors – more towards NF-kB]

Sites of Receptors :
① TLR – Plasma membrane / Endosome [↑ both ILR 3 & NF-kB]
② CLR – Plasma membrane [usually only NF-kB]
③ RLR – Cytosol
④ NLR – Cytosol

* End result of NLR pathway → Activation of IL-1β (through Caspase-1)

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* **Adapter Protein for** a) TLR → MyD 88
  b) NLR → Caspase 1

* **Pyrin gene mutation** (NLR – AIMS2) → Familial Mediterranean fever

	TLR	CLR	RLR	NLR
① Location:	Plasma membrane/ Endosome	Plasma memb.	Cytosol	Cytosol
② Ligands:	- Triacyl Peptide - Diacyl Peptide - LPS - Flagellin - ds RNA - ss RNA - DNA	- Mannans - β-1,3 glucan	- Short ds RNA - long ds RNA	- Flagellin - Peptidoglycan DNA/RNA Candida - dsDNA
③ Adapter:	- MyD 88 (use except TLR3) - TRIF/ TRAM	SYK	IPSP FADD	ASC (CARD)
④ Signal transduction	- IRAK-1 - IRAK-4 ↓ NFkB ↑ ± IRF 3 ↓ ↑ IFN α ↓ IL-1 IL-18 TNFα IL 6 MLP-1	LARD-9 ↓ ↑ NF-KB	TRAF 3 ↓ ↑ NF-KB	ASC + CARD ↓ ++ Caspase ↓ ProIL1β → IL-1β ↑ IL-1β ↑ Gasdermin D (creates pores in PM & ultimately l/t destruction of the cell

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Other PRPs :

① RAGE – DAMP receptor
– Plasma membrane
– recognises advanced Glycogen End Products

② NOD-1 / NOD-2 – intracellular / cytosolic receptors
↓ Peptidoglycan ↓ Muramyl dipeptide

Adapter Protein – RIP 2 (+)
⇓
↑ NF-kB
↓
↑ Cytokines

* NOD 1 / 2 don't follow Inflammosome pathway

⇒ NOD-1 → IBD-1 gene
CARD-15 (Chr 16) → mutation l/t Chron's disease
Blau Syndrome

'PRR' DEFECTS :

PRR defect		Infections
① MyD88 / IRAK 4 (AD)	→	Pyogenic bacteria
② TLR 3 (AD)	→	HSV Encephalitis
③ TLR 5 (AR)	→	Listeria
④ DECTIN-1 (recognises βD glucan) (AR)	→	Candida / trichophytons
⑤ CARD9	→	Candida
⑥ MBL (Mannose Binding Lectin) (AR) (Complement Activation Defect)	→	Bacteria / fungi
⑦ NOD2	→	Chron's disease
⑧ NLRP3 (AD)	→	Autoinflammatory Synd.

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AUTO-INFLAMMATORY SYNDROMES:

AUTO INFLAMMATORY SYND.	AUTO IMMUNE SYND.
→ defect of Innate Immunity → No MHC association	→ Defect of Adaptive Immunity → MHC association +++

Clinical features –
1. Skin / Mucocutaneous
2. Musculo Skeletal Symptoms
3. ± Fever
4. ± Other Symptoms

Types:

1. **Periodic / Recurrent fever Syndromes:**
   - Skin
   - Musculoskeletal
   - Fever
   - Other

1. **TRAPS** – TNF receptor associated Periodic fever syndrome (TNF Rα mutation) (AD)
2. **FMF** – Familial Mediterranean Fever (AR) (MEFV mutation) – Pyrin
3. **HIDS** – Hyper IgD Syndrome (AR) (MVK mutation)
4. **PFAPA** – Periodic Fever Aphthous Stomatitis Pharyngitis Adenopathy (Marshall Syndrome)
5. **AOSD** – Adult Onset Still's Disease (Acquired) (equivalent to SOJIA – Systemic Onset Juvenile Inflam. Arthropathy)

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② Cryopyrinopathies :

- All are d/t NLRP3 (AD) mutation
- Urticaria
- + Others

① FCAS – Familial Cold Auto Inflamm Syndrome } → No SNHL / Uveitis (<1 yr age)

② MWS – Muckle Wells Syndrome → SNHL / Uveitis ✓ (>1 yr age)

③ NOMID / CINCA – Neonatal Onset Multi-systemic Inflamm. Disorders
– Chronic Infantile Neurologic Cutaneous Articular Syndrome
} → SNHL / Uveitis ✓ (<1 yr age)
→ CNS involvement ✓

③ Pyogenic Disorders : – no fever

Genes – ① PAPA – Pyogenic Arthritis Pyoderma Gangrenosum & Acne (PST PIP 1 mutation) (AD)
– no Osteomyelitis

② MAJEED (LPIN2 mutation) (AR) } – Psoriasis / Recurrent Osteomyelitis (has features of both CRMO & PAPA)

③ CRMO – Chronic Recurrent Multifocal Osteomyelitis (AR)
– Recurrent Osteomyelitis

④ Miscellaneous :

① Granulomatous Syndromes –

a) Chron's disease (intestinal features) → not inherited ← { Arthritis, Uveitis, Skin inv.

b) Blau Syndrome (no intestinal features) → inherited (AD)

② DIRA – Deficiency of IL-1RA (Osteomyelitis / Pustular lesions / Periosteitis)

③ DITRA – Deficiency of IL-36R antagonist (Chronic Pustular Psoriasis)

} Pustular diseases

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Features of Periodic / Recurrent fever Syndromes:

(Cause of death = Cardiac Amyloidosis ⇓ Arrhythmias)

	Symptom Duration	Symptoms
① TRAPS –	1-3 wks	→ Chronic recurrent serositis (Infants)
② FMF –	1-3 days	→ Serositis (abd. pain) / Scrotal swelling (Teenages) → very high risk of Amyloidosis
③ HIDS –	3-7 days	→ ↑Ig D / ↑Ig A / Cervical adenitis (<2yrs)
④ PFAPA –	4-5 days every 4 wks	→ Cervical adenitis + Aphthous ulcers [Rx by Tonsillectomy]
⑤ AOSD –	Daily (Quotidian fever)	→ Age > 16 / Daily fever (>1 wk) / Salmon rash / Arthritis / ⊕ Lymphadenopathy / Hepatosplenomegaly – ↑↑ Ferritin – Yamaguchi Criteria

SUMMARY:

① They have Mendelian Inheritence (except PFAPA & Chron's)

② Age – Infancy / Childhood (except – FMF / Chron's)

③ No fever – Pyogenic syndrome

④ Durations of fever –
- Daily – AOSD / SOJIA
- ≤ 1 day – FCAS
- 1-3 days – FMF / MWS
- 3-7 days – HIDS / PFAPA

⑤ Max. CNS involvement – NOMID / CINCA

⑥ Amyloidosis – FMF

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(7) All Autoinflamm. syndromes are d/t IL-1β cytokines

(8) Rx – (i) IL-1 antagonists – Etanercept (TNF α ⊖) ⇒ for TRAPS

Rilonacept } (IL-1 ⊖) + Canakinumab (typical for cryopyrinopathies)
Anakinra }

(ii) Steroids

(iii) Colchicine (for FMF)

(iv) Tonsillectomy (for PFAPA)

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Humoral Mechanisms of Innate Immunity

HUMORAL MECHANISMS :

Humoral Mechanisms
- Acute Phase Reactants
  - Positive APR
  - Negative APR
- Complements
  - Classical Pathway
  - Mannose Binding Lectin (MBL)
  - Alternate Pathway

ACUTE PHASE REACTANTS :

① Positive APR : (Increase)

① Complements – C3/C4/C9

② Coagulating/Fibrinolytic agents – Fibrinogen
Plasminogen
tPA
Protein S
Plasminogen Activator Inhibitor-1 (PAI-1)

③ Transport/Storage – Ferritin (Fe)
Ceruloplasmin (Cu)
Haptoglobin (Free Hb)
Hemopexin (Free Heme)

* Bacteria uses Fe for its metabolism – if free Fe ↑
* Free Fe causes free radical damage to our system.

To prevent this, Free Fe is ↓ by ↑ Ferritin

④ Anti-Proteases – Antichymotrypsin
Pancreatic Secretory Trypsin ⊖ (PST ⊖)
α₁ Antitrypsin

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⑤ **Others** –
1. C-reactive Protein
2. IL-6
3. TNF α
4. Phospholipase-A
5. LPS-BP (Lipo Poly Saccharide Binding Protein)
6. G-CSF
7. Sr. Amyloid A
8. α_1 Acid Glycoprotein
9. α_2 Microglobulin
10. Copper
11. Procalcitonin
12. cortisol
13. C_1 INH (C_1 ⊖)

CRP –
- Ⓝ – 6mg/dl [<6mg/dl → CRP -ve]
- t½ – 24 hrs
- functions –
  1. ↑ Opsonisation
  2. ↑ Phagocytosis
  3. ↑ within 6-12 hrs of any injury/inflammation
- non-specific
- we can't tell the type of injury

② **Negative APR** :
1. Albumin
2. Transthyretin (TTR)
3. Thyroid Binding Globulin (TBG)
4. AFP (α fetoProtein)
5. Insulin like Growth Factor (IGF)
6. α_2 High Sensitivity GlycoProtein (α_2 HSGP)
7. Retinol Binding Protein (RBP)
8. Antithrombin
9. Fe/Zn/calcium

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COMPLEMENT SYSTEM:

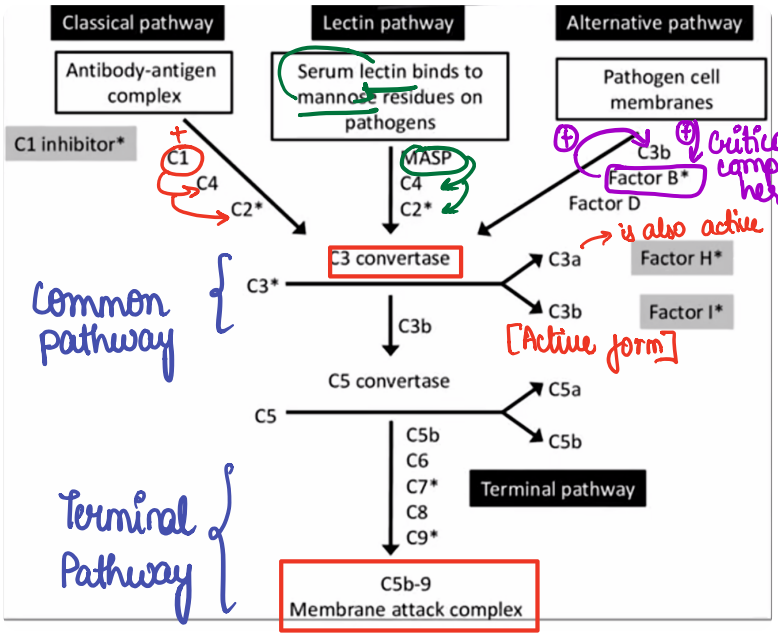
→ Intravascular components

Activated by

Types – ① Classical pathway ⟹ Ag-Ab complex
② Alternate Pathway ⟹ Mannose
③ MBL Pathway ⟹ Bacterial components

Antibodies as activators → IgM > IgG > IgA [IgD & IgE]
(max.)
they don't activate complement

Simplified version of Complement Pathways:



→ MASP – MBL associated serine Protease

→ C3 convertase:

a) In classical & MBL pathway } – C_2bC_4b

b) In Alternate pathway } – C_3bBb

[C_3b in case of alternate pathway forms C_3 convertase & this C_3b comes from Classic & MBL pathway]

Factor D:

→ Factor D activates factor B into Bb & Ba.

$$\text{Factor B} \xrightarrow[\text{Factor D}]{} Bb + Ba$$

↓

binds to C_3b & forms C_3 convertase

Properdin: → binds Bb & C_3b together

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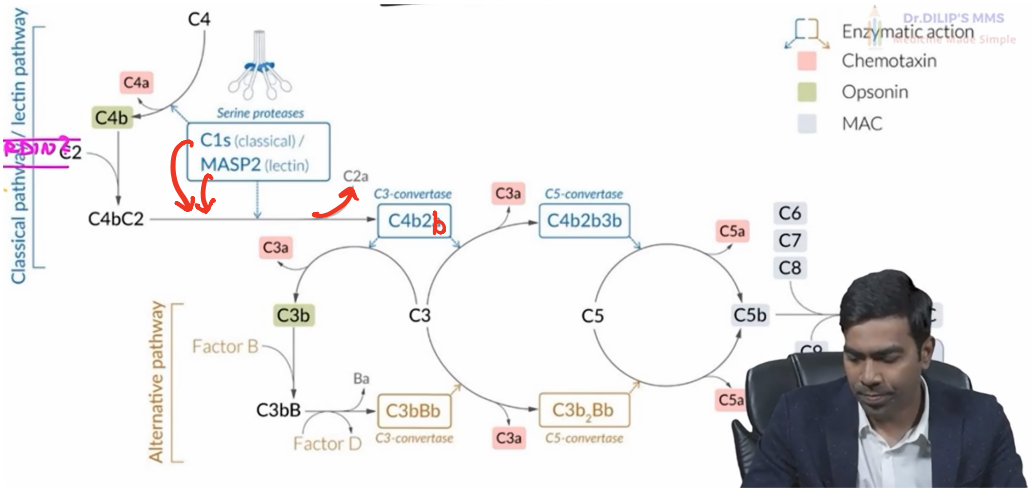

① C1 complement :

⇒ C_1 — C_{1q} — 6 subunits
— C_{1r} — 2 subunits
— C_{1s} — 2 subunits
} 10 subunits (proteins)

Units

→ C_{1q} is activated by Ag-Ab complex

→ Ab binds to Ag ⟹ conformational change ⟹ ⊕ C_{1q} first

→ Chemoattractants / Chemotaxins / Anaphylotoxins } ⟹ C_{3a} & C_{5a} [$C_{5a} > C_{3a}$]

→ Opsonins ⟹ C_{4b} & C_{3b} [$C_{3b} > C_{4b}$]

→ Opsonisation – Coating of cells, so that they can be recognised by Phagocytes

* most powerful opsoniser among Ig → IgG

Primary Effects Of Complement Pathway :

① Opsonisation by C_{3b}/C_{4b} (IgG)
② Lysis by Membrane Activation complex (C_{5b-9})
③ Activation of Mast cells / Granulocytes – by $C_3/C_4/C_5$
④ Chemotaxis by $C_{5a}/C_{3a}/C_{4a}$
⑤ Clearance of Immune Complexes ⇒ by $C_{3b} > C_{4b} > C_{5b}$ (Important of Pathogenesis of SLE)

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Regulators of Complement System:

Regulators

Cell Surface

① CD 55 [Decay Acceleration Factor - DAF] → ⊖ C_3 convertase

② CD59 [Membrane Inhibitor of Reactive Lysis - MIRL] → ⊖ MAC/TAC

③ CD46 [Memb. Cofactor Protein - MCP]
CD35 [Complement Receptor - I] → ⊖ Alternate Pathway [Similar to Factor H/I]

GPI anchored proteins → If defective ⇓ PNH

Fluid Phase

① Classical pathway regulators
② Alternate pathway regulators
③ C_5 regulations

Fluid Phase Regulators:

[C_5 regulation → See in the next pages]

Classical Pathway Regulators

① C_1 INH (C_1 esterase)
↓
⊖ C_1 / ⊖ FXIa / FXIIa / ⊖ Kallikrein

Alternate Pathway Regulators

→ Factor H / I

HC_3b — Factor I → IC_3b (Inactive)

↓ C_3b ⊕ Properdin

C_3b ← Factor B ← ⊕ Bacterial components

↓

C_3bB ← Factor D

Ba ← ↓

C_3bBb (C_3 convertase)

↓

C_3 → C_3b → C_3bBb3b (C_5 convertase)

↓

C_5 → C_{5b} → C_{5b-9} (TAC/MAC)

Factor H:
- downregulates C_3b
- Acts as a cofactor
- Factor H binds to C_3b & gives to Factor I
  ↓
  Factor I then binds to C_3b making C_3b inactive

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C_1 INH DEFICIENCY:

C_1 INH ↓ ⊖ → ↑ Kallikrein ⊕ → High Molecular wt. Kininogen → ↑↑ Kinins ↑ (Bradykinin) → ↑↑ vascular Permeability ↑ → Angioedema ± urticaria

ACE ↓ ↓ Neprilysin → degrade Bradykinin

ACE ⊖

Neprilysin ⊖ (Sacubitril)

Angioedema c̄ Urticaria is seen in Type I HSR

Conditions causing C_1 INH deficiency:

1. Congenital (Hereditary Angio Edema - HAE)
2. Acquired (SLE / CLL)

Rx:

1. Acute → Berinert (r C_1 INH) [Best Rx]
   Fresh Frozen Plasma (alternative)
2. Prophylaxis (Chronic) → Icatibant (Bradykinin receptor ⊖)
   Ecallantide (Kallikrein ⊖)

Angioedema

- c̄ urticaria → Type I HSR
  - Rx – 1. Antihistamines
    2. Steroids
    (± Adrenaline)
- ± Urticaria → Bradykinin excess
  - Drug-induced → Rx – Discontinue the drug
  - C_1 INH def. → Rx – Acute – Berinert / FFP
    Prophylaxis – Icatibant, Ecallantide

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DEFECTS OF FACTOR H/I :

① deficiency of Factor H/I ⇒ +++ Alternate pathway
(loss of function mutation)

② Gain of function of mutation of Factor D/B ⇒ +++ Alternate Pathway

③ C_3NeF ⇒ +++ Alternate Pathway [Stabilises C_3 convertase]

Effects : ① Complement related HUS (atypical HUS) → d/t ① & ②
② Complement mediated MPGN (MPGN II/III) → d/t ③

Dense deposit disease ← MPGN II
no Dense deposit disease ← MPGN III

C_5 REGULATORS : (FLUID PHASE)

① Clusterin
② Factor I
③ Protein S

Anti-C_5 → Eculizumab (MAb)
↓
Blocks activation of MAC

DYSREGULATION OF COMPLEMENTS :

Cell Surface Comp.
① PNH
↓
can be treated
c̄ Eculizumab (Before giving this, we need to give Meningococcal vaccine because it blocks MAC activation)

Fluid phase
① Angioedema
② Complement related HUS
③ Complement mediated MPGN

COMPLEMENT DEFICIENCY :

① C_{1q} → ① SLE → Nephritis / CNS / Photosensitivity

② ↑ Infections → Encapsulated bacteria

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	SLE	Infections
② C_{1r}/C_{1s}	Nephritis	Encapsulated bact.
③ C_4	Nephritis + Multi Organ dysfunction (MOD)	Encapsulated bact.
④ C_2	Photosensitivity / articular involvement	Encapsulated bact. + Pyogenic bact.
⑤ C_3	Malar rash Photosensitivity Arthralgia Raynaud	Pyogenic bact.
⑥ C_5-C_9	Multi Organ Dysfunction	Neisseria Infection

* Alternate pathway deficiency will not cause SLE

CH 50 :

→ indicator of complement activity

→ Pts. serum c̄ suspected excess complement, is put in sheep RBC & % of lysis is seen.

CH50	Complement levels	Interpretation
↑	↓ (comp. consumption)	↑↑ complement activity
↓	↓	complement deficiency

Basics of Adaptive Immunity

T cells → BM ← B cells

BM → lymphoid precursor

✓ NOTCH signalling → T-cell lineage → leave BM → Thymus (Thymocytes)

NOTCH signalling ✗ → B-cell lineage → stay in BM → BM (mature

	T-cell lineage	B-cell lineage
% in Blood	→ 80% (CD4 > CD8 = 2:1)	→ 20%
Lymphomas	→ T-cell lymphomas 15%	→ B cell lymphomas (85%)
Tissue distribution	→ Perifollicular (LN) (cortex) – Periarteriolar area (spleen)	→ Follicles (Germinal centre) – LN / spleen / GIT / Respi. tract
Surface markers	→ CD3 (Pan T cell) CD2 CD4/CD8 CD6 CD7	→ CD19 (Pan B cell) CD20 CD22 CD9 – Pre B CD10 – Precursor B CD79a / CD79b
Receptors	→ TCR α/β → α/β γ/δ → γ/δ	→ BCR – Ig [IgM/IgD] IgH IgK or Igλ
Function	→ CMI → CD4 → 'Helper' ↳ CD8 → 'Cytotoxic' T cell	→ Humoral – Ab production

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LYMPHOID ORGANS :

① Primary Lymphoid Organs :

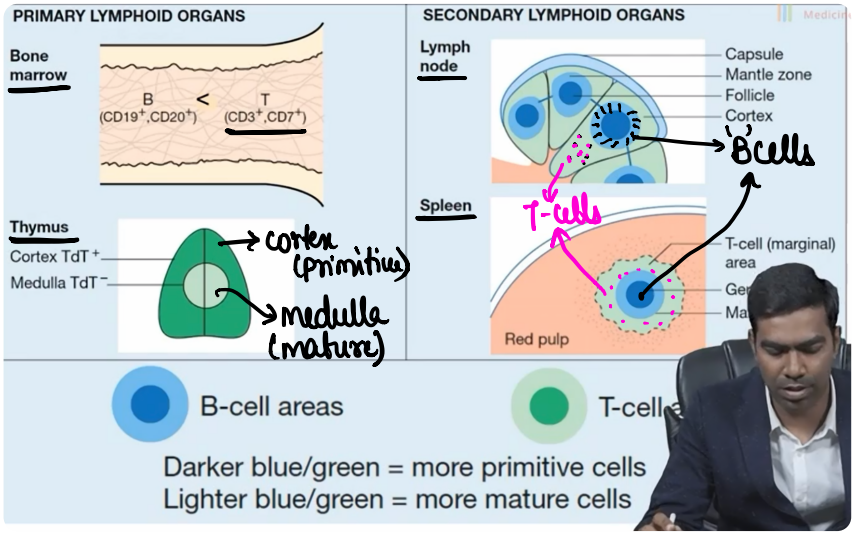
- forms / matures lymphocytes
- eg: BM
  Thymus

② Secondary Lymphoid Organs :

→ activates lymphocytes
→ adaptive response

- Simple organs → ① Diffuse (MALT) ② Solitary (Intestinal mucosa) ③ Aggregates (Peyer's patches)
- Intermediate Organs → Tonsils
- Proper Organs → Lymph node, Spleen

Centre – mature
Periphery → Primitive



⇒ Centre – primitive
Periphery – mature

PRIMARY LYMPHOID ORGANS :

① Bone Marrow

② Thymus → produces 'T' cells
→ location – Superior anterior mediastinum (Retrosternal / Precordial)

Children – Thymus is large → On CXR – Thymic sail sign

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- Adults - thymus involutes ⇒ age dependent atrophy

→ Histology - Thymus cortex - immature T cell
Medulla - mature T cells } → Mesoderm (thymocytes)

- Thymic epithelial cells
- Macrophages
- Dendritic cells

→ Embryology - originates from - 3rd/4th arches (Endoderm)

→ thymocytes - mesodermal
thymus epithelial cells - Endodermal

→ Clinical - ① Hypoplasia - Di-George Syndrome/ SCID (Severe Combined Immuno deficiency)

② Hyperplasia - 2° to Chemo Rx / Steroids

③ True lymphoid hyperplasia (Autoimmune)

④ Thymic Ca. - (rare)

⑤ Thymoma:

↓

- Anterior mediastinal mass
- Age: 40-60 yrs
- Symptoms: Chest pain / Cough / SOB / Superior Vena Cava Synd. (SVC Synd.)
- ± Paraneoplastic Syndromes:
  a) Myasthenia Gravis
  b) Pure red cell aplasia
  c) Immunodeficiency c̄ thymoma
- Rx - Surgery ± Chemo - RT

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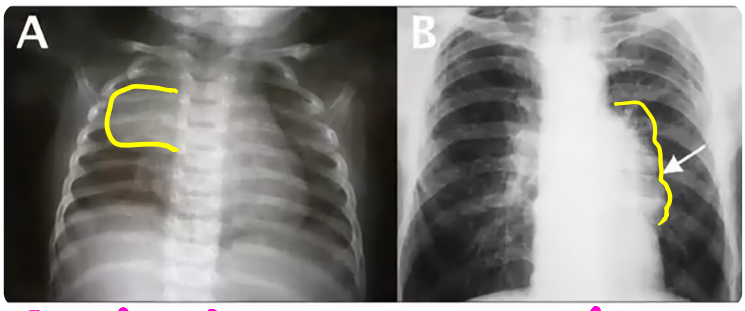
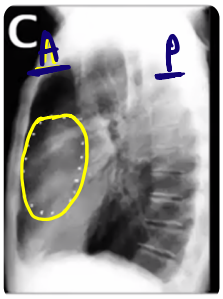
* D/D of Anterior Mediastinal Mass:

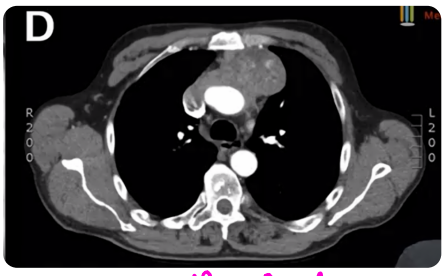
'4Ts' → Thymoma / Thymoma Ca.
Thyroid (Retrosternal Goitre)
Teratoma
Terrible Δ → lymphoma
Aortic aneurysm



Thymic sail sign — PA view



Lateral view

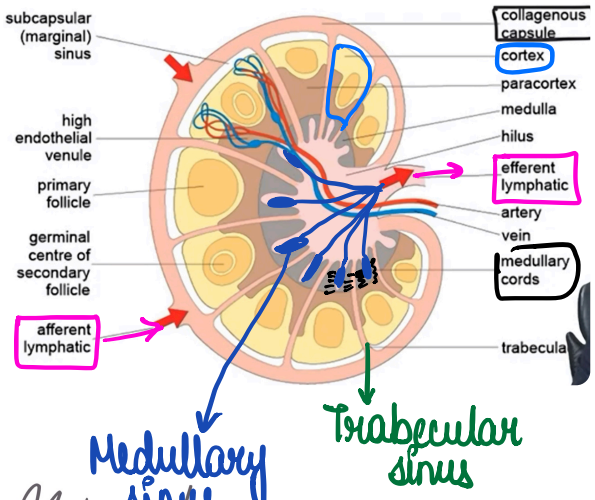


Ant. Mediastinal mass on CT scan

↓
- clear vascular markings of mediastinal structures are seen
- anterior mediastinal mass grows over the mediastinal structures; but, doesn't push them.

SECONDARY LYMPHOID ORGANS:

① Lymph Node:



① Cortex – B-cells (follicles)
② Paracortex – T-cells (perifollicular)
③ Hilus – lymph comes out from efferent lymphatic through hilus
④ Follicles – 1° – Inactive B-cells (naive)
2° – Active B-cells

→ mantle zone (dark) → naive B cells
→ Germinal centre (pale) → active B cells

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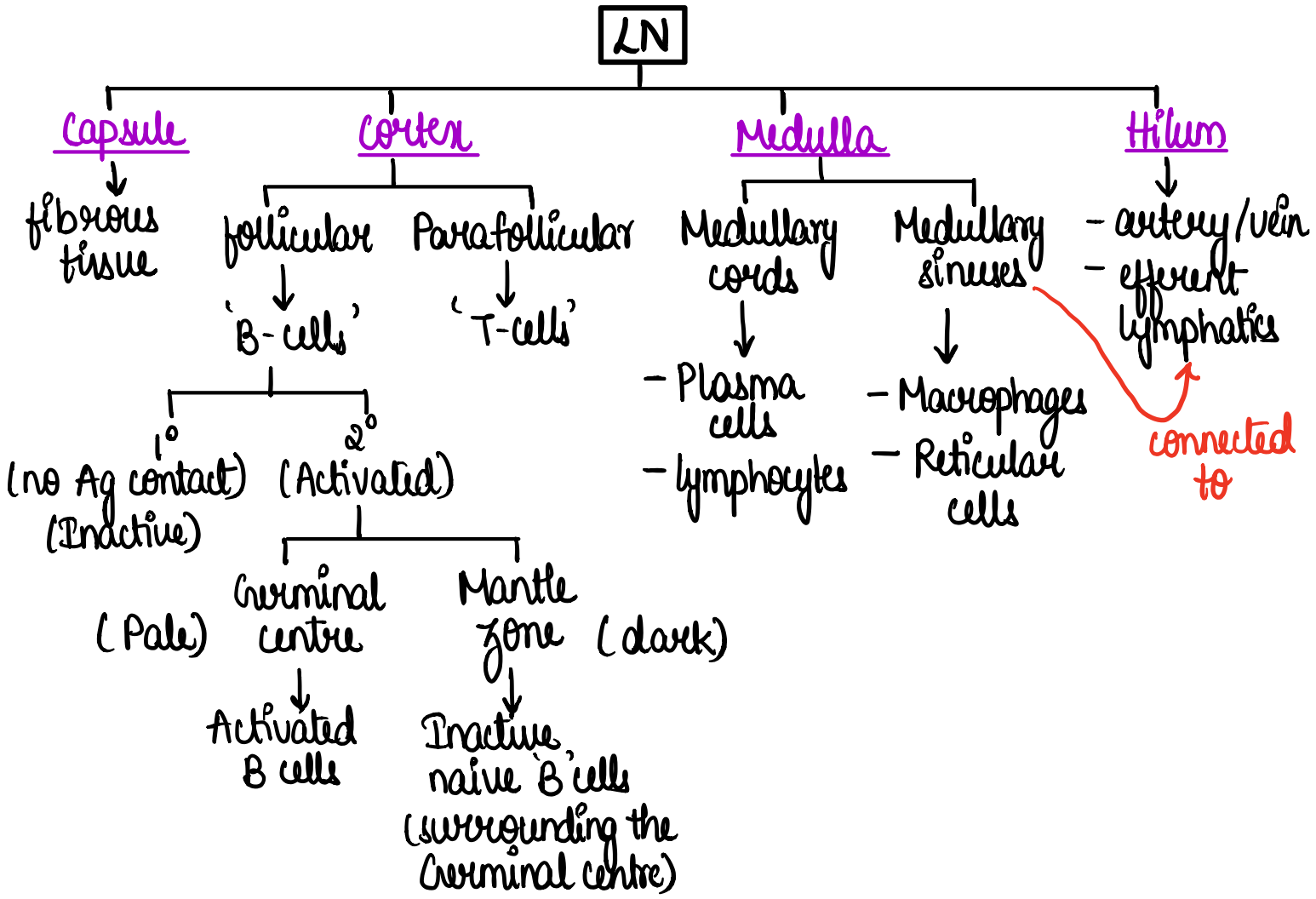
⑤ **Medullary cords** – has Plasma cells (short-lived), Macrophages & lymphocytes

⑥ **Medullary sinus** – connected to efferent lymphatics
– has macrophages & Reticular cells

⑦ **Trabecular Sinus** – takes the lymph from afferent & gives it to efferent lymphatics
– formed by capsule



* **Enlarged Thymus** ⟹ USG → is done & Hilus of Thymus is looked for

- **Present** → Reactive hyperplasia, Infections, etc
- **Distorted** → Lymphoma/Mets.

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Lymphadenopathy : [MIAMI Criteria]

Etiology – ① Malignancy – Lymphomas
Leukemias
Metastatic Cancers

② Infections – a) Viral – EBV/ HIV/ HSV/ CMV
VZV/ Measles
Rubella / Hepatitis

b) Bacterial –

(i) Generalised – ≥ 2 groups of LN + non contiguous
↓
- Brucellosis
- TB
- Syphilis
- Atypical mycobact.
- Leptospirosis

(ii) Localised – 1 group of LN
↓
Streptococci
Staphylococci
Cat Scratch Disease
Tularemia

③ Autoimmune – Connective Tissue Disorders (SLE/ RA)

④ Iatrogenic – Drugs – Allopurinol / Phenytoin (Pseudo lymphoma)
- Atenolol
- Captopril
- Gold
- Penicillins
- Quinidine
- Cotrimoxazole
- CBZ (carbamazepine)

MIAMI criteria :

M – Malignancy
I – Infection
A – Autoimmune
M – Miscellaneous
I – Iatrogenic

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⑤ Miscellaneous – Castleman dis.
Kawasaki dis. (Kikuchi)
Rosai Dorfman dis.

Lymph node Bx:

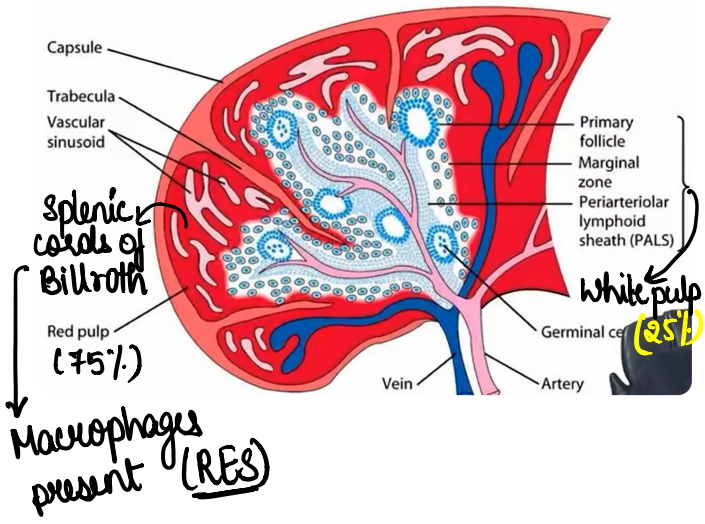
Indication – Age > 40
– Size > 2cm
– Locations – esp. - Supraclavicular
– Duration – > 1 month
– Presence of 'B' symptoms
– + Hepatosplenomegaly

for Lymphoma → Excision Biopsy is preferred over FNAC

Consistency of LN: (not reliable)

① Hard / Non-tender / fixed → Metastasis
② Soft / firm → Infections
③ Rubbery → Lymphoma

② Spleen:



Functions of Red pulp:

a) Senescent RBC – kills
b) Fetal erythropoiesis (upto 2-7 months of fetus)
c) Platelet sequestration (1/3 of platelets)

① White pulp:

a) Primary follicle → 'B' cells
b) Marginal zone → Marginal zone are found physiologically only in spleen
c) Periarteriolar lymphoid sheath – 'T' cells

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SPLEEN

- **Red Pulp** (75%)
  1. Sinusoids
  2. Billroth cords (RES) – macrophages + Platelets
- **White Pulp** (25%)
  1. Follicles – 'B' cells
  2. Peri Artireolar Lymphatic Sheath – 'T' cells

  ⇓ sites of adaptive immunity / immune reaction
- **Marginal zone**
  - Marginal zone B cells

Splenomegaly:

Etiology –
1. RES hyperplasia ⇒ Hemolytic anemia (Red pulp)
2. Immune hyperplasia ⇒ a) Infections (White pulp)
   - Viral
     - EBV
     - HIV
     - CMV
   - Bacterial
     - TB
     - Mycobact. Avium Complex
     - Leishmaniasis (visceral)
   - Parasitic
     - Malaria

   b) Autoimmune – Connective Tissue Dis. [RA / SLE]
   - RA → Felty Syndrome
3. Malignancies – MPN [ET / PV / PMP / CML]
   - Lymphomas / Leukemias (HL / NHL / HCL)
   - Large Granular Lymphocytic Leukemia
   - Myeloma

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④ Congestion – Cirrhosis
Portal vein/Splenic vein
CHF
Schistosomiasis

⑤ Infiltration – Lysosomal storage [Gaucher's/Neiman-Pick]
Glycogen storage
Histiocytosis X (LCH)
Splenic cysts

Massive Splenomegaly:

① Thal. major
② Malaria
③ Kala-azar
④ Mycobact. Avium complex
⑤ Felty Syndrome
⑥ Schistosomiasis
⑦ MPN
⑧ Lymphomas (esp. CML)
⑨ Gaucher's dis.

Quantification of Splenomegaly:

	Weight	Clinical	USG (length)
① Normal →	<250g	Impalpable	<12cm
② Mild →	400-500g	<3cm	12-14cm
③ Moderate →	750-1000g	3-8 cm	14-18 cm
④ Massive →	>1000 g	>3 cm [(or) crosses umbilicus – Spleen enlarges towards Rt. hypochondrium]	> 18 cm

CT scan:

– single most accurate measure of S+

– Splenic width (AP) ⇒ >10.5 cm
Cranio-caudal ⇒ >14.6 cm

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Hypersplenism :

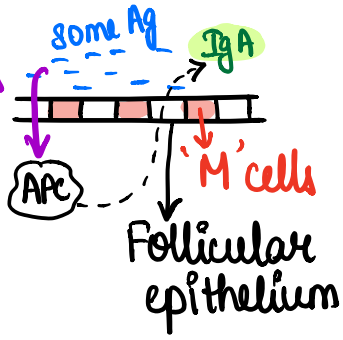
→ causes ↑ sequestration
↑ Phagocytosis

→ Cytopenias ⟹
① Anemia (m/c)
② ± leukopenia
③ ± thrombocytopenia
} can have Pancytopenia in long-run.
④ + B.M hyperplasia
⑤ + Splenomegaly

⇓
Improves after Splenectomy

③ MALT : [Mucosa Associated Lymphoid tissue]

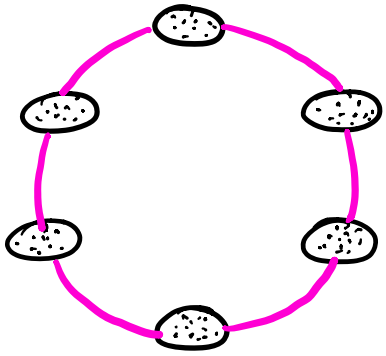
① Peyer's Patches / Intestinal mucosa
② Tonsils
} Transcytosis



④ Tonsils :

Pharyngeal tonsil [Adenoids] ⇒ no crypts → Respiratory epithelium

'WALDEYER'S RING'



Tubal tonsil (lateral wall of nasopharynx) → Prominent crypts

Palatine tonsil → Prominent crypts
↓
Non-Keratinised Squamous epithelium

Lingual tonsil (shallow crypts) → Non-Keratinised Squamous epithelium

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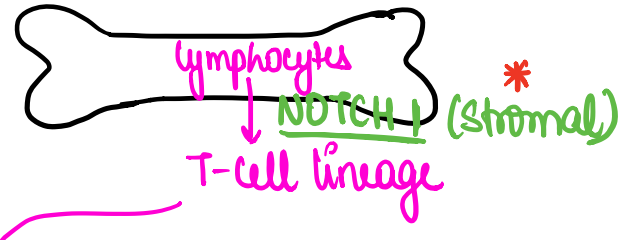
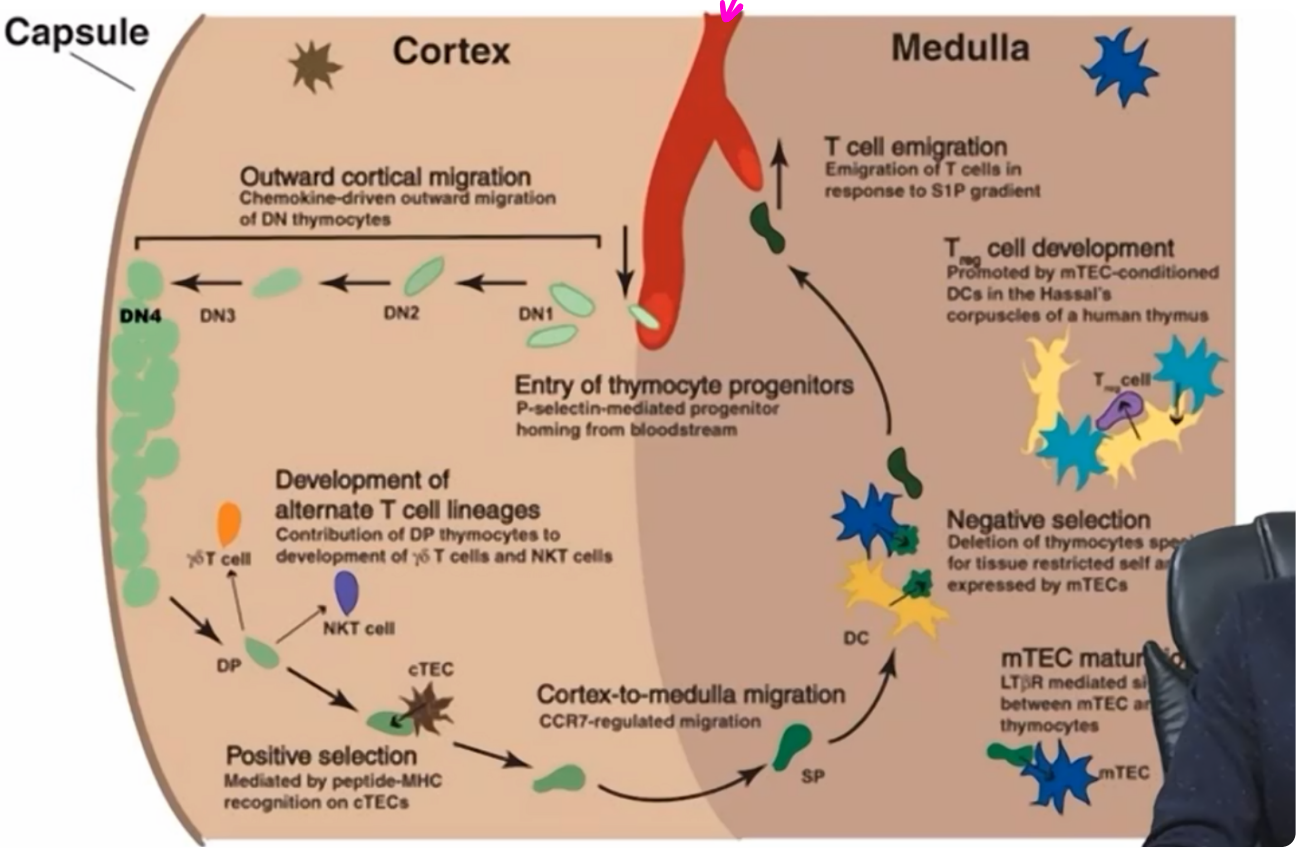
T- cells basics and beyond

T-CELL DEVELOPMENT:





Lymphocytes formed in BM

↓ NOTCH 1

Enter Thymus (Thymocytes)

↓

Thymocytes enter cortico-medullary junction through High Endothelial venule mediated by PSGL-1 [Endothelial P-selectin] expressed by T-cells

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↓

Outward Cortical migration

Thymocytes migrate outwards & are double negative (DN) [CD4−/CD8−]

↓

Proliferation of migrated T cells

T cells now become Double Positive [CD4+/CD8+] & migrate from cortex to medulla

↓

Development of alternate T cell lineages

DP T cells : ① αβ T cells (>95%) → m/c

Alternate : ② γδ 'T' cells, ③ NK 'T' cells } 5-10%

Though they are DP T cells, they are CD4−/CD8−

↓

Positive selection

(m/c pathway chosen by DP 'T' cells)

[αβ 'T' cells undergo '+ve' selection while alternate lineages don't undergo any selection

	DN1	DN2	DN3	DN4
CKit	+	+	+	−
CD44	+	+	−	−
CD25 (IL2Rα)	−	+	+	−

DN1 – Committed 'T' cell Progenitor

DN2 – VDJ rearrangement (β/γ/δ)

DN3 – Pre T cells

DN4 – Proliferating pre 'T' cells

T cells

- MHC restricted [CD4+/CD8+] → Classic DP 'T' cells → αβ 'T' cells
- non-MHC restricted [CD4−/CD8−] → alternative lineage → CD1d restricted
  - + → NK 'T' cells
  - − → γδ 'T' cells

– different from NK cells

– they lie b/w NK & T cells

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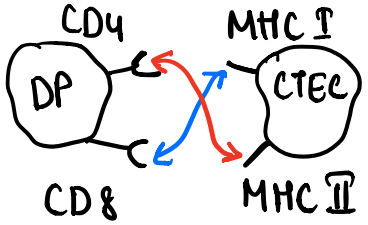
Positive selection

[tells whether 'T' cell can properly bind to MHC or not]

→ αβ 'T' cells interacts c̄ cortical thymic epithelial cells (cTEC)



[eg: If CD8 binds to MHC I, the T cell downregulates CD4 & becomes CD8 T cell]

- CD_4 binds to MHC II → CD4+ & CD8 − (T Helper cell)
- CD_8 binds to MHC I → CD8+ & CD4− (T cytotoxic cell)

↓

If it doesn't bind to any one of them (MHC I/II)

↓

Apoptosis (>90%)

→ Purpose of Positive selection is to find out the functional 'T' cells

→ End result → Single positive functional T cells are formed [either CD4+ (or) CD8+]

αβ 'T' cells	γδ 'T' cells
① MHC restricted ↓ CD4/CD8 Initial − Both ✓ Later − CD4 (or) CD8	① Non-MHC restricted ↓ CD4− CD8− [+ not C_{1d} restricted]
② Binds to MHC Ag	② −
③ Adaptive immunity	③ Innate imm.
④ >90-95%	④ 5-10%
⑤ undergo Positive selection in thymus	⑤ −

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↓

Cortex-to-Medulla Migration

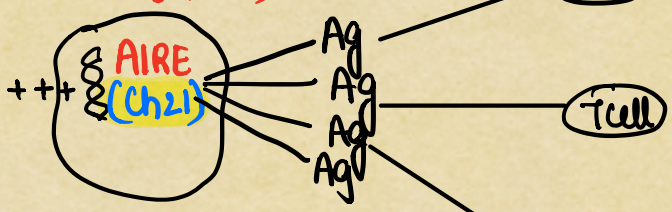
These positively selected SP T cells migrate from cortex to medulla regulated by CCR-7

↓

Negative Selection

→ occurs in Hassal's corpuscles
→ to prevent autoimmunity
→ this is mediated by mTEC

Auto immune regulatory gene (AIRE)



[mTEC (medullary TEC)
mDC (medullary DC)]
- They express the above Ag in various tissues
- These Ag constitute 10% of genome

T cell → Moderate interaction → Regulator T cells (CD4+ Treg) (FOXP3↑↑↑) ⇒ Exit!

T cell → Strong interaction → Self reactive (Deleted) ⇒ Don't Exit

T cell → Weak interaction → Survive! ⇒ Exit
↓
effector T cells → CD4, CD8

↓

T cell migration

Survived effector T cells / Tregs (3-5%) move out of Thymus in response to Sphingosine 1 Phosphate gradient

* **FINGOLIMOD**
→ ⊖ Sphingolin 1 Phosphate
→ T cells cannot move out of lymphoid organs & are sequestred there
→ used in Multiple Sclerosis

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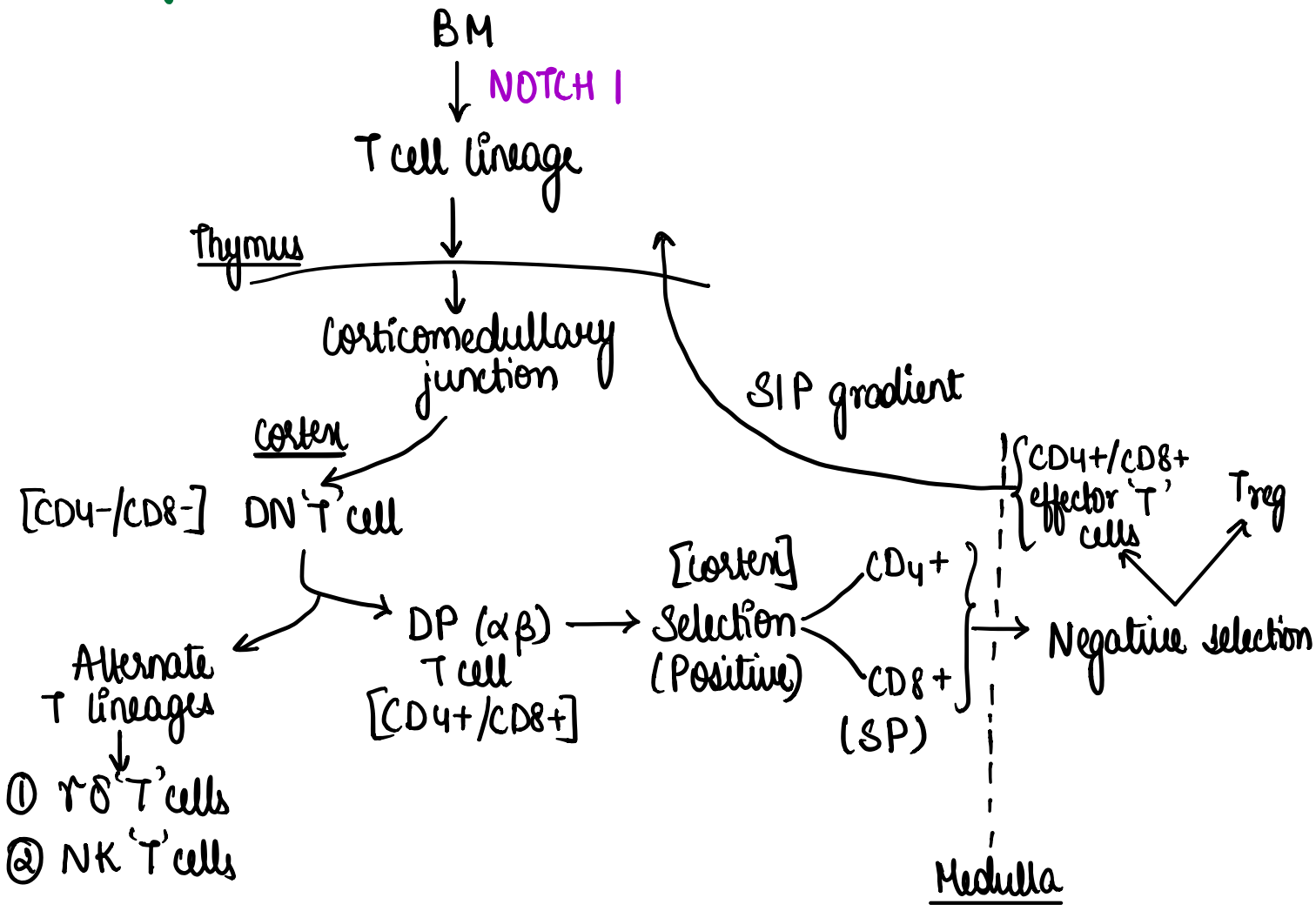
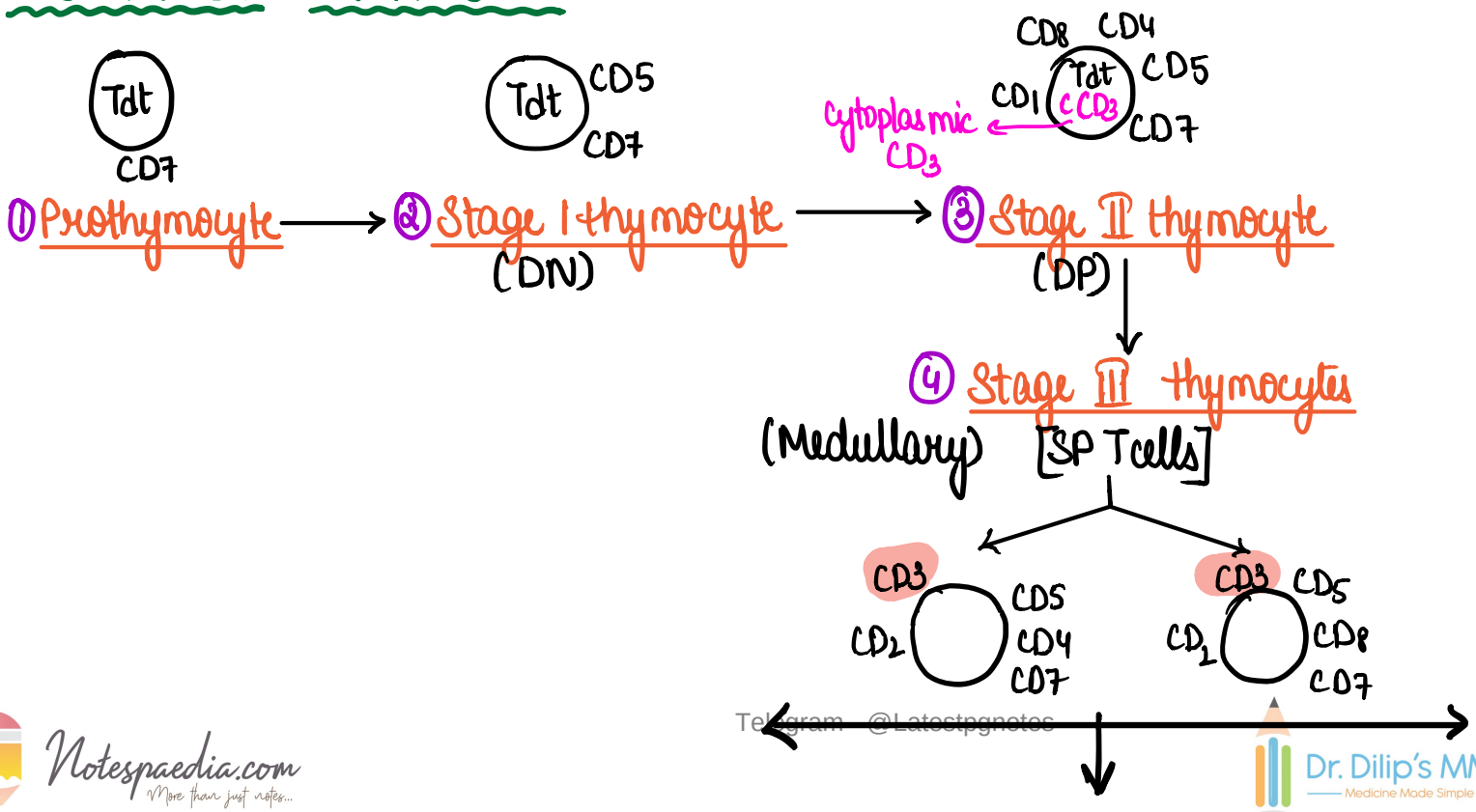
Summary of T-cell development:



SURFACE MARKERS:



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Negative selection

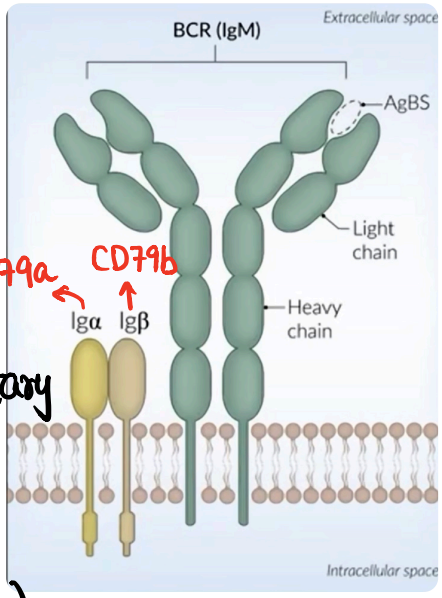
⑤ Effector T cells

CD3, CD2, CD5, CD4, CD7 — weak expression — CD4+ T cell

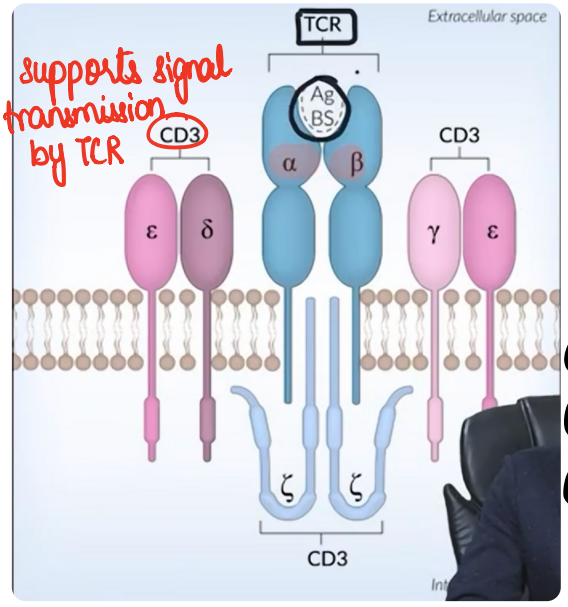
CD3, CD2, CD5, CD8, CD7 — weak expression — CD8+ T cell

* CD3 ↓ Pan T cell marker

B CELL (VS) T CELL RECEPTORS :



CD79a, CD79b → Complementary receptors (support signal transmission)



supports signal transmission by TCR

CD3 : ↓ 3 subunits ↓ ① ε-δ ② ζ ζ ③ γ ε

	BCR	TCR
① Ag binding	→ macromolecules (lipids/ proteins/ carbohydrates) ↓ 5-15 Aa size (5-7 nucleotides sequences) ↳ 5-7 monosacch.	→ Ag presented by APC (Short Aa sequences) CD4 (12-17 aa) CD8 (8-12 aa)

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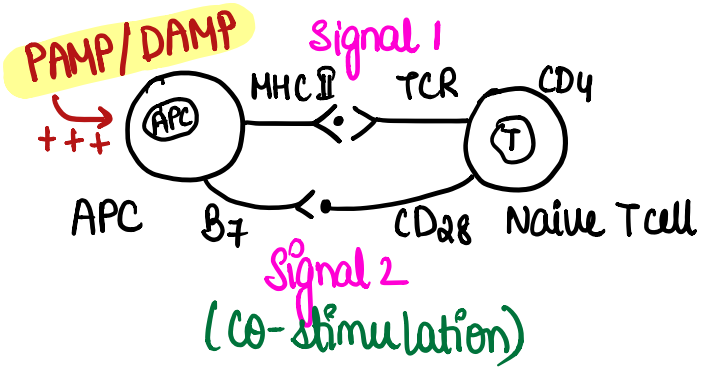
	BCR	TCR
② Chains	④ chains (Ig)	② chains
③ Ag binding sites	2	1
④ Secretion of receptors	+++ (possible) [as Abs]	– (not possible)
⑤ Response to Ag	Changes over time	no change
⑥ Diversity	$>10^9$ clones	$>10^{11}$ clones (more)
⑦ Signalling	Ig α → CD79a, Ig β → CD79b	CD3
⑧ Coreceptors	CD19, CD21 (CR2), CD81	CD4 (or) CD8
⑨ Epitope type	Confirmational & linear	Linear only
⑩ Co-stimulation	–	+

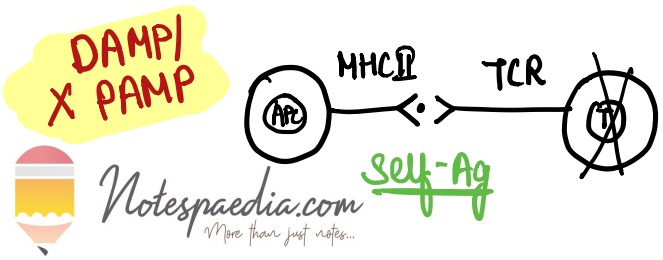
T CELL STIMULATION :



Only Signal 1 → Anergy!
[T cell not dead immediately, but doesn't bind to any receptor as long as it lives]

* Expression of B7 by APC is the key feature

Signal 1 + Signal 2 → T cell activation



Autoreactive → Anergy

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Peripheral tolerance:

PAMP - Pathology associated molecular pattern
DAMP - Damage associated molecular pattern
} needed for Signal 2

→ If there is no signal 2 & only MHC II is expressed without expressing B_7 ⟶ this indicates the absence of DAMP/PAMP
⇓
indicates that T cell is binding to self-Ag.
⇓
This is prevented by sending the T cell into Anergic state

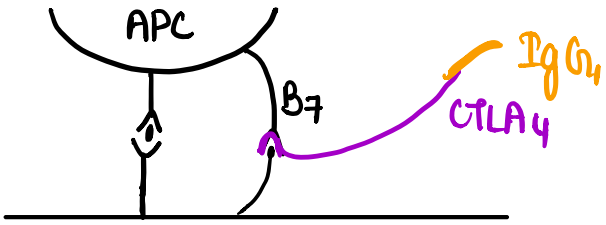
This whole process is called Peripheral Intolerance

* Central intolerance occurs by negative selection in medulla of thymus.

3-SIGNAL MODEL:

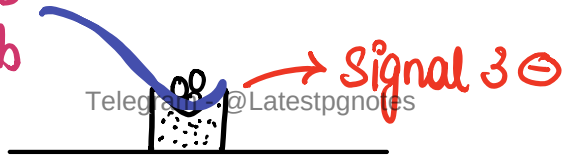
→ Cyclophillin – attaches to Cyclosporine ⇒ ⊖ Calcineurin
→ FKBP – attaches to Tacrolimus [FK 506] ⇒ ⊖ Calcineurin

→ CTLA4 → Cytotoxic T lymphocyte Ag4 ⇒ natural anti B_7 molecule
↓ released by Cytotoxic T cells



⇓
We can add IgG1
⇓
CTLA4 fusion protein
not Mab { Abatecept, Belatecept

→ ILR-2R ⊖ (Anti CD25) ⇒ Basiliximab, Daclizumab



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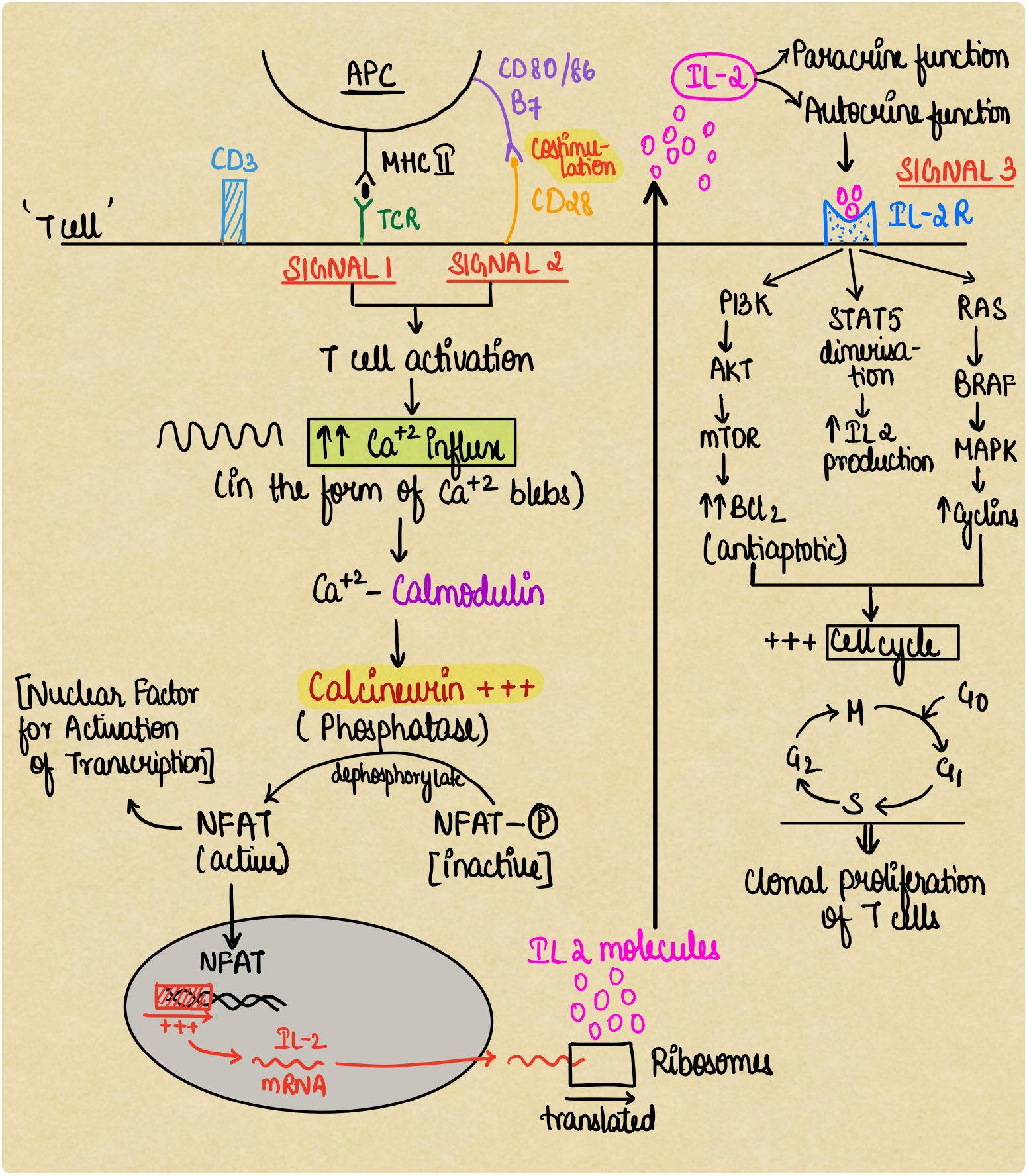
3 - Signal Model



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→ mTOR ⊖ → Sirolimus (Rapamycin), Everolimus } ⇒ ⊖ cell cycle

---

→ Immunosuppressants → Azathioprine, Leflunomide, Mycophenolate Mofetil } ⇒ ⊖ cell cycle
(Inositol Monophosphate dehydrogenase ⊖)

→ OKT3 / Muromonab (IgG type) → Opsonizes i.e. Fc of this IgG binds to FcγR III of Splenic macrophages (NK/Phagocyte) ⇓ Kill the T cell by the release of granzymes/perforins
(anti CD3)

Done through Anti-thymocyte Globulin (ATG)

→ This is called 'Killing / Depleting Ab' (because they ↓ T cell population)

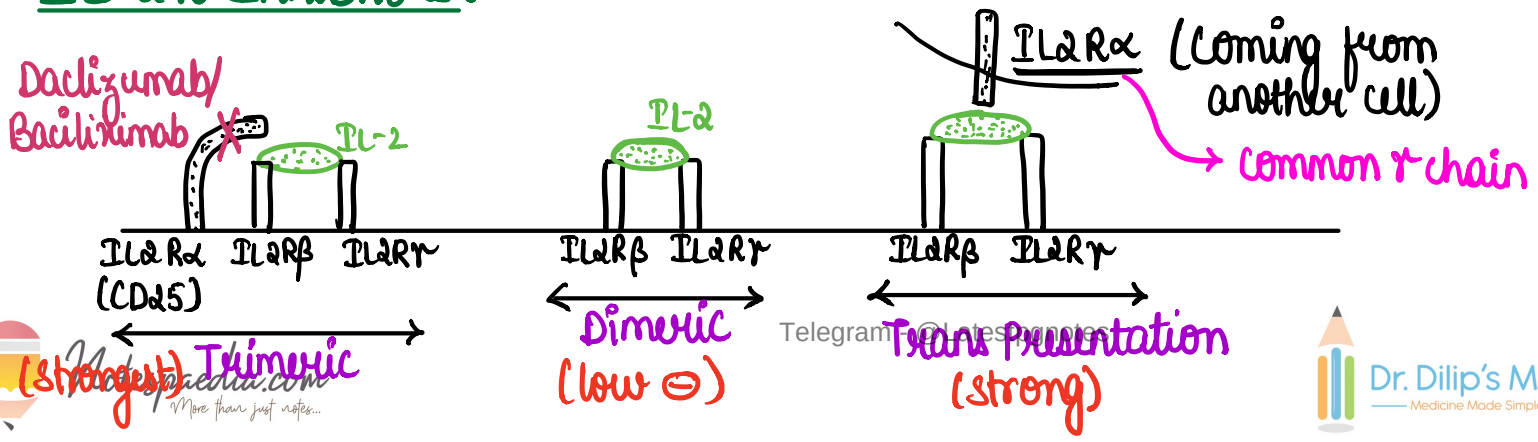
→ Basiliximab, Daclizumab } → 'Non-depleting Ab'

→ Non-T cell specific ⊖ :

① CD 20 – → B cell ⊖ → Rituximab

② CD 52 – → B + T cell ⊖ → Alemtuzumab [used in SLE / Multiple Sclerosis]

IL-2 R Inhibitors :



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T-CELL SUBTYPES:

① Th1 Pathway:

IL12Rβ IL12Rα
P40 | P35
IL-12

APC (macrophage/DC) — Intracellular Ag — Naive 'T' cell → T bet → Th1 Cell (activated)

Transcription factor that pushes Tcell towards Th1 pathway

Th1 Cell (activated) → IFNγ / IL-2 → +++ Macrophages

activates & recruits them

clonal proliferation of Th1 cells

+++ Macrophages → IL-1 / TNFα

① fever
② loss of appetite/wt
③ Powerful chemotactin (+++ PMN)

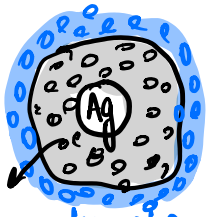
[* IL 12 tells Tcell that it is an intracellular Ag]

Clinical Applications:

① Infection c̄ intracellular organisms (mycoplasma/Salmonella)
② T1 DM / RA / MS

Kill & Eliminate

Can't kill → Atleast contain the Ag → Granulomatous response



macrophages — lymphocytes

[TNFα is the signature CK of granulomatous reaction]

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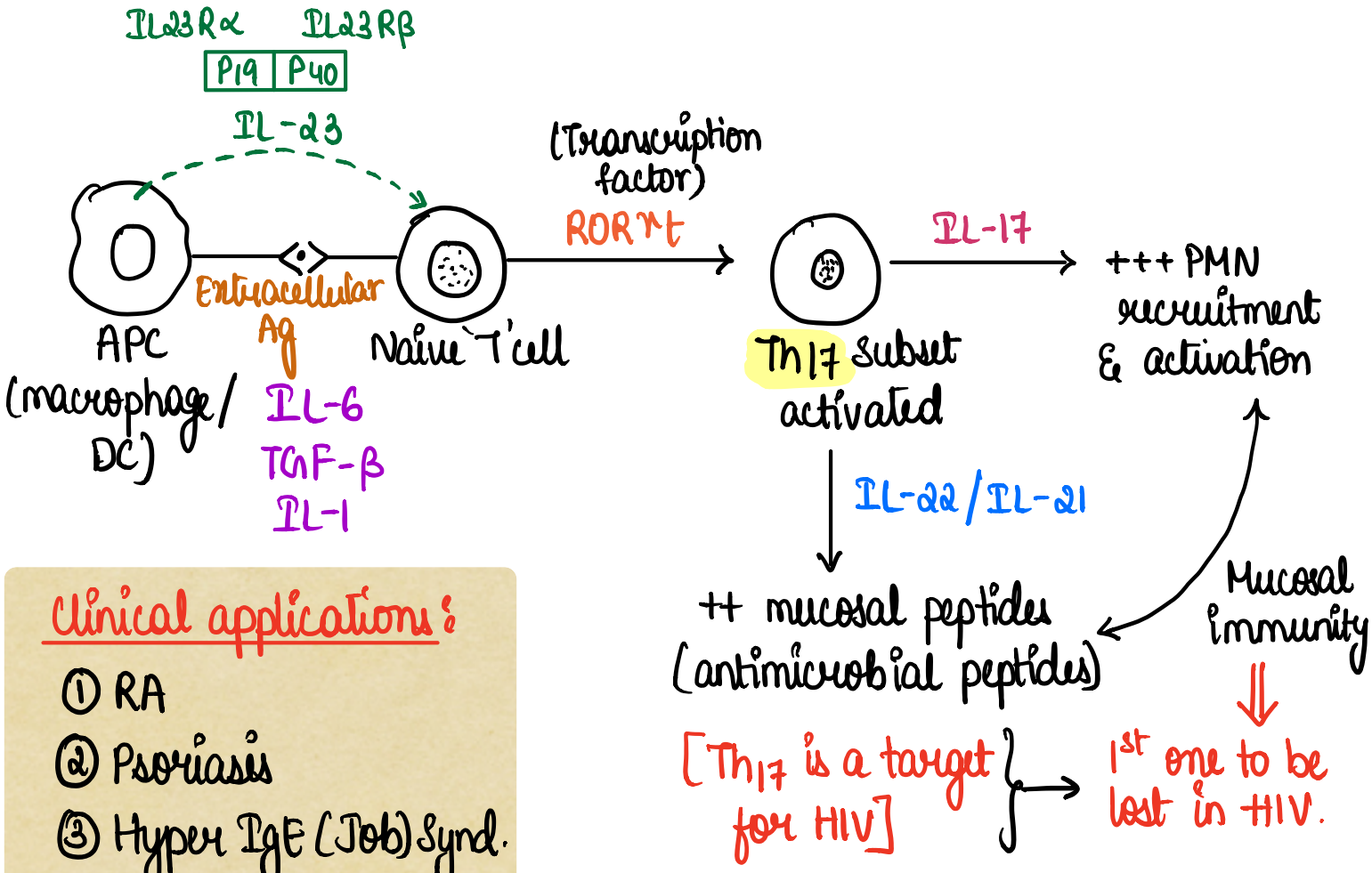
② Th17 Pathway:

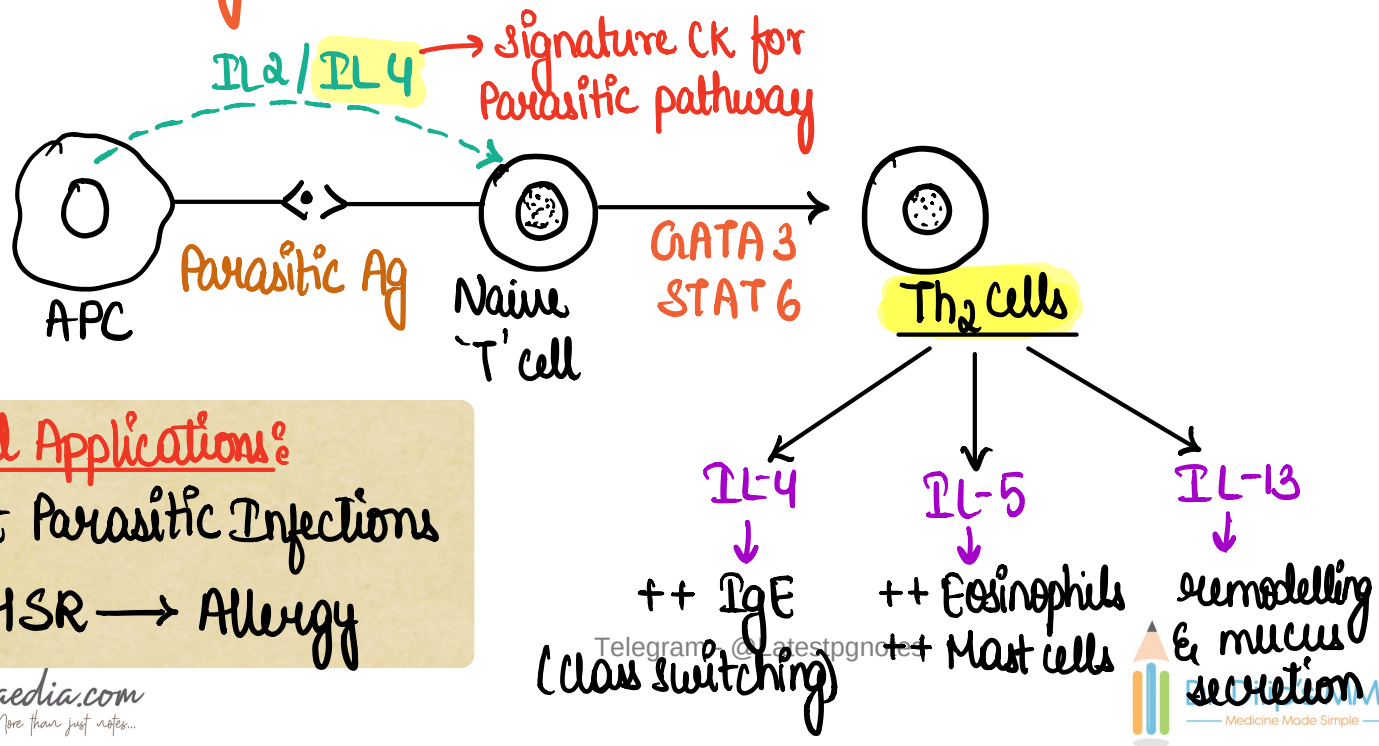


Clinical applications:

① RA
② Psoriasis
③ Hyper IgE (Job) Synd. [STAT 3 deficiency]

---

③ Th2 Pathway:



Clinical Applications:

① Fight Parasitic Infections
② T_1 HSR → Allergy

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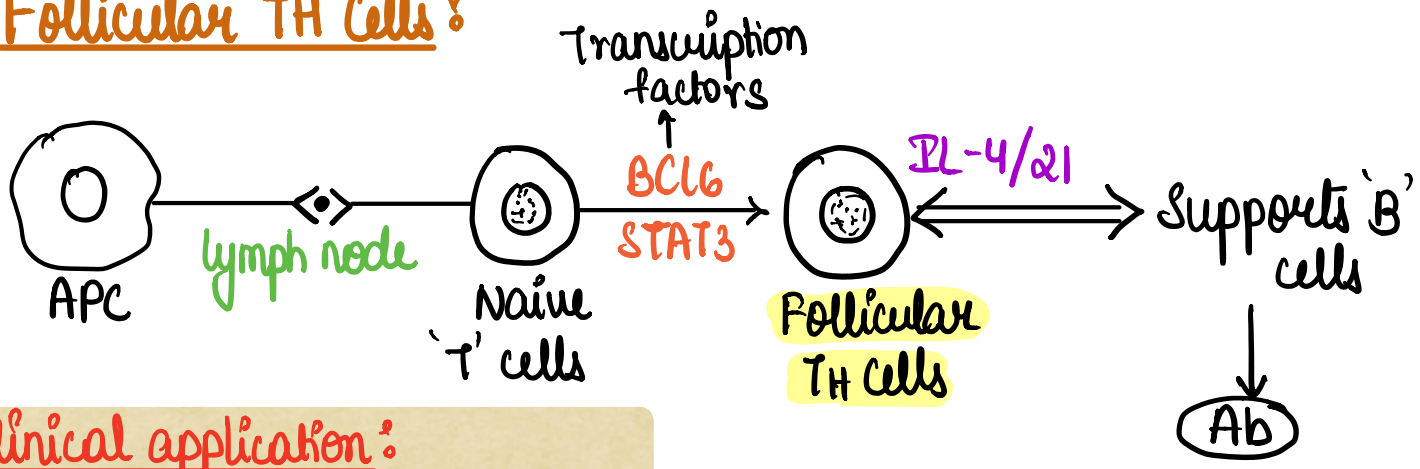
④ Follicular TH Cells :

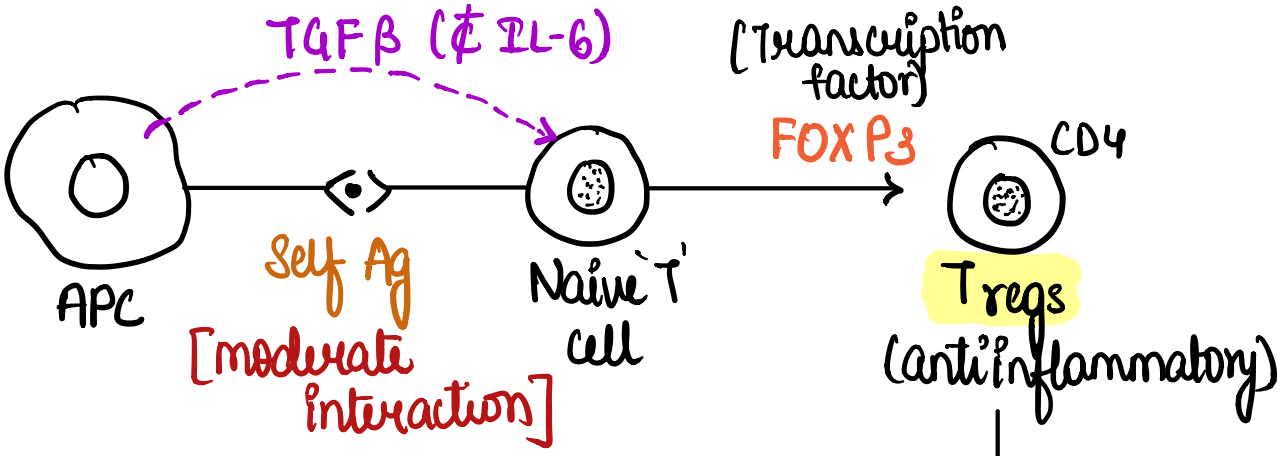


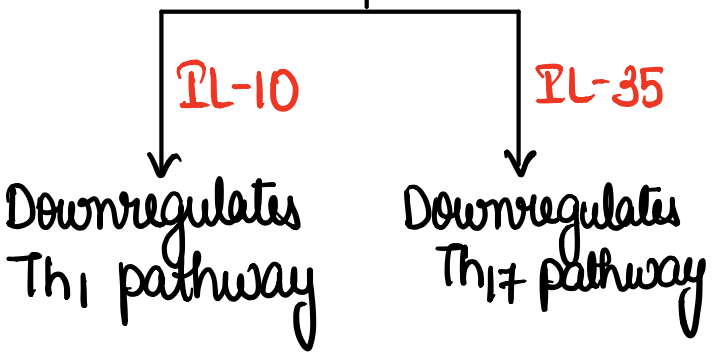
Clinical application :

① Autoimmune disorders

---

⑤ TReg (Regulatory) Pathway :





Clinical application :

① FOX P3 mutation
⇓
IPEX syndrome
[Neonatal IBD like picture]
a) Neonatal DM
b) ↑ susceptibility to infections
c) Chronic diarrhoea

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TARGETED THERAPIES:

① TNFα ⊖:

① Infliximab
② Etanercept
③ Adalimumab
④ Golimumab
⑤ Certolizumab (Pegylated form also available)

② IL-1 ⊖:

① Anakinra
② Rilonacept
③ Canakinumab

Uses – ① Gout
② Autoinflammatory dis.

③ IL-6 ⊖:

① Siltuximab ⟶ Use – Multicentric Castleman Disease
② Elsilimomab

④ IL-6R ⊖:

① Tocilizumab ⟶ Use – RA.

⑧ IL-12 ⊖ + IL-23 ⊖:

① Ustekinumab [Blocks P_{40} subunit]

⑨ IL-23 ⊖:

① Risankrumab
② Guselkumab
③ Tildrakizumab

} [P19 ⊖]

Use – Psoriasis

⑩ IL-17 ⊖:

① Secukinumab
② Ixekimumab
③ Bimekizumab

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⑨ IL-17 R⊖:

① Brodalumab

⑩ IL-4⊖:

① Pitakinra
② Pascolizumab
③ Dupilumab

⑪ IL-5⊖:

① Mepolizumab
② Reslizumab

⑫ IL-5 R⊖:

① Benralizumab

⑬ IL-13⊖:

① Lebrikizumab

⑭ Anti-IgE:

① Omalizumab

⇓

Uses – ① Can be used in Asthma (BA) & Allergies

② IL-5⊖ can also be used be used in Churg-Strauss Synd. (caused by Eosinophils)

T-CELL MARKERS:

Effector T cell

- CD4+, CD8−, CD3+
  - Th_1 → CXCR3, CCR5
  - Th_{17} → CCR6, CCR4
  - Th_2 → CRTH2, CCR3, CCR4
  - F_{TH} → CXCR5, PD-1
- CD8+, CD4−, CD3+

Treg

CD8−
CD4+
CD3+
FOXP3+++
CD25/127+

γδ T cells

CD8−
CD4−
CD3+
RORγT+

NK T cell

CD8−
CD4−
CD3+
IFNγ/IL4+

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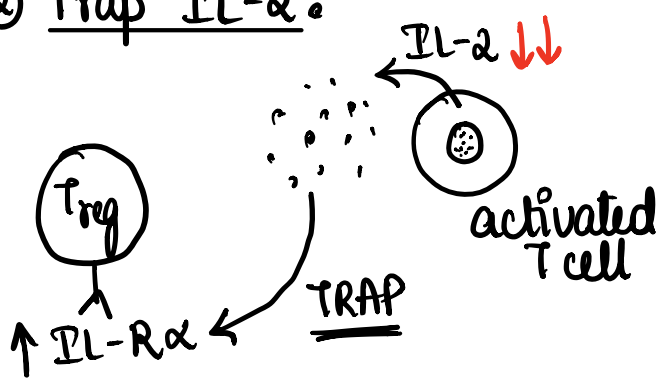
Mechanism of anti inflammatory action by Treg cells:

① Anti inflamm. cytokines:

a) IL-10 ⟶ ⊖ Th_1

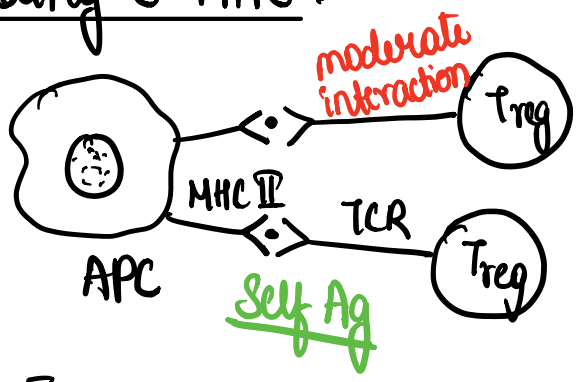
b) IL-35 ⟶ ⊖ Th_{17}

② Trap IL-2:



* Treg Cell has ↑ IL-Rα that binds c̄ the IL-2 released by activated T cell
⇓
↓ IL-2 (Trapping)
[↓ activation of other cells by IL-2]

③ Binding c̄ MHC:



[not available for binding c̄ self reactive T cell]

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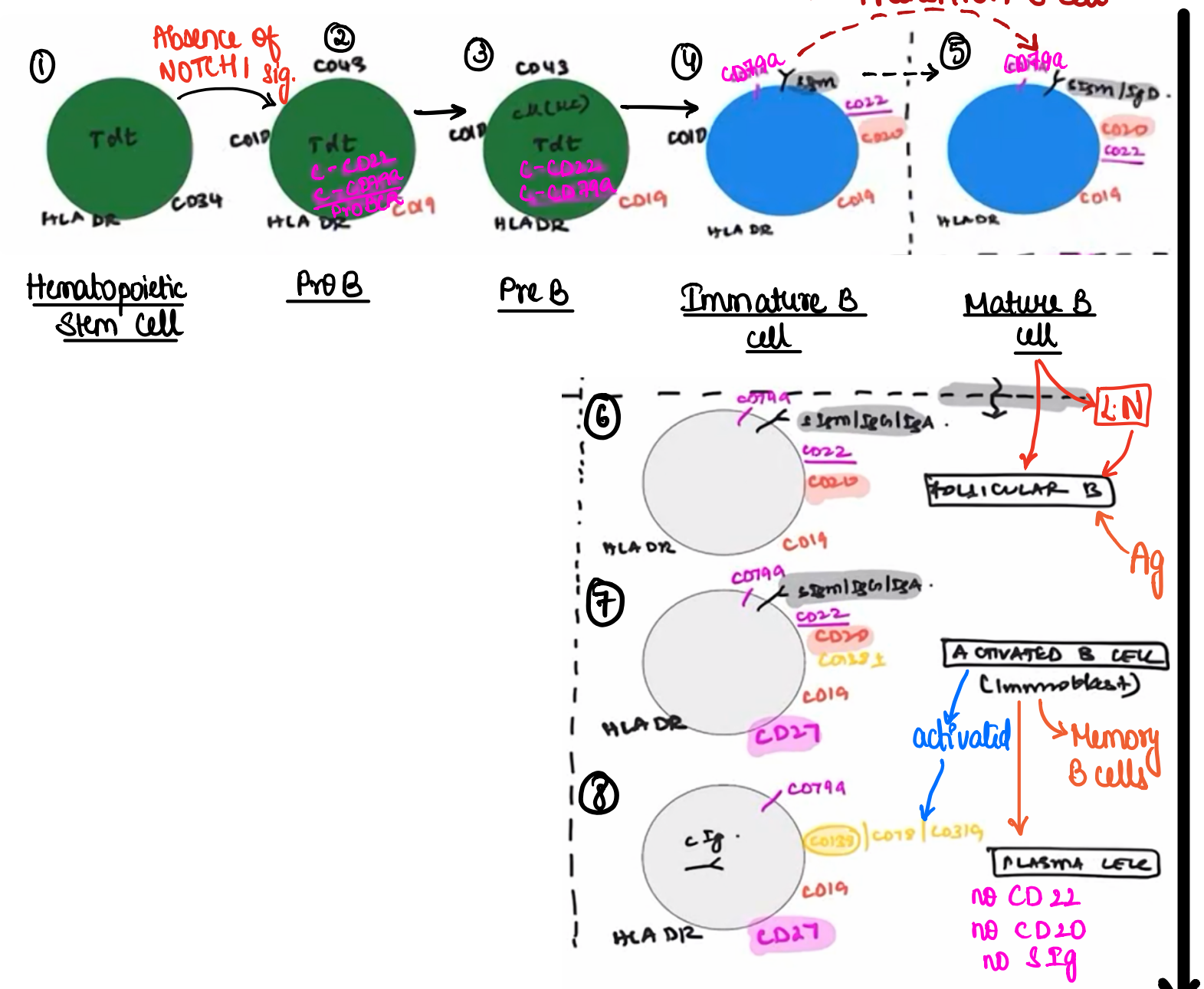
Basics of 'B' cells - I

Ag independent stages (BM)

* Transition B cell



Ag Dependent stages (Peripheral)

* Transitional B cell:

T_1 B cell (in blood) → T_1 → T_2 → Marginal zone B cells

T_1 → T_3 (Apoptosis)

T_2 → Follicular B cells (future) → Mature B cells

Spleen

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Pre-B cell: → no surface Ig

↓

Positive selection [in late Pre B] → Surface Ig ✓

↓

non-self Ag Exposure → Does not bind to Ag → BCR → non-functional → Deleted

↓

(B-cell Receptor) BCR becomes functional [binds c̄ Ag]

↓

Survives

Immature B cell:

↓

Negative selection

↓

Self Ag Exposure

- Strong Binding → Option
  - Apoptosis / Anergy
    - Multi Valent Ag
    - Soluble Ag
  - Receptor editing → fails → Apoptosis / Anergy
  - Receptor editing → Do not bind → Survive
- no strong binding → Survive

Activated B cell (Immunoblast)

↓

Centroblast [no SIg]

↓

Centrocyte [produces SIg]

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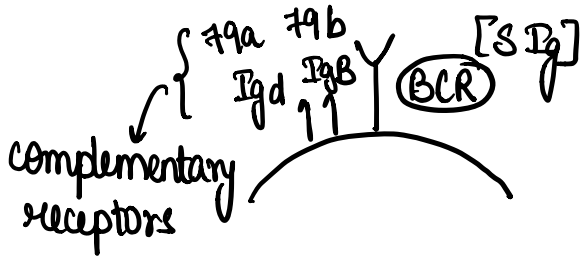
MARKERS :



① CD 34 → Hematopoietic Stem Cell

② CD 43 → Pro B cell
Pre B cell

③ CD19 → Pan B cell Marker

④ c-CD 79a → Pro BCR → only complementary receptors are seen here, no surface Ig are expressed
(Cytoplasmic CD 79α)

⑤ Cytoplasmic μ (cμ)
[Surrogate Light Chain] (SLC) } → Pre BCR (only light chains are expressed)

⑥ Centroblast → doesn't express SIg

⑦ Centrocyte → expresses SIg

⑧ Plasma cell → they don't express surface Ig (SIg). Instead they produce cytoplasmic Ig (cIg) - Ab.

⑨ * SIg starts getting expressed from Immature B cell

⑩ CD22 → Starts being expressed as cytoplasmic CD 22 @ Pro B cell
↳ then comes onto the surface from next stage i.e. Pre B cell
→ Plasma cell → no CD 22

⑪ CD 20 → seen in 'selected B cell' (after Pre B cell)
→ Plasma cell → no CD 20.
→ Pro & Pre B cells → no CD 20

⑫ CD 27 → only activated B cells have CD 27 → Activation Marker

⑬ CD 138 / CD 78 / CD 319 → Plasma cell Markers
(Classic Plasma Cell Markers)

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(14) CD 138 – sometimes, activated B cells also show CD138

(15) CD22 & CD79a → go hand in hand, from late Pre-B cell stage

(16) (N) Plasma cell → No CD20
No CD22 CD79a ✓
No SIg

(17) Malignant Plasma cell → they will lose CD 79a also

(18) CD 45RO → Memory B cell
(also CD27 +)

CD 27 – Activation marker

CD20 – all B cells except Primitive B cells & Plasma cells

CD79a – All 'B' cells ⟺ CD22 → absent in Plasma cells
- Primitive → cytoplasmic
- all others → surface

CD19 – all 'B' cell lineages (surface) [Pan B cell marker]

SIg – all 'B' cell lineages except
- Primitive
  - Pro B (Pro BCR) [Igα · CD79a] [Cytoplasmic]
  - Pre B (Pre BCR) [SLC – Surrogate Light Chain] (Surface)
- Plasma (cytoplasmic Ig → cIg)

CD 130 – Activated B cells ± Plasma cells

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[Only in BM] →	CD10	CD34	CD23	CD93 [transitional B cell marker]	CD45RA
T_1 B cell	+	+	−	+	+
T_2 B cell	+	+	+	+	+
Mature B cell	−	−	+	−	+

→ Activated B cells (CD38+)

- Plasma cells (CD38+)
- Memory cells
  - CD19+
  - CD27+
  - CD38−
  - CD45RO+

B_2 Cells
↓
B cells coming out from BM follicular B cells & splenic marginal zone B cells

Fetal Hematopoiesis:

HSC
↓
'B' cells → B_1 (innate) → seen in Body cavities (pleural / pericardial fluid, etc)

	B_1 cells	B_2 (follicular)	B_2 (Marginal)
1st time production	Fetus	After birth	After birth
Prevalence	<5 %	70-80%	15-20%
'V' region	Restricted	Diverse	Partly restricted
Renewal	self renewing	No self renewal (short lived)	No self renewal (long lived)

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	B_1 cells	B_2 (follicular)	B_2 (Marginal)
Primary location	Body cavities	Follicles (LN/Spleen)	Marginal zone (spleen)
Spontaneous Ig production	↑↑	↓	↓
Ig (secreted)	IgM >> IgG	IgG >> IgM	IgM >> IgG
Ab affinity	low	High	Intermediate
Plasma cells	Short lived	Short lived / long lived	Short lived / long lived
Carb. Ag	+	−	+
Protein Ag	−	+	+
T cell dependency	− (T-cell independent)	+ (dependent)	+/−
Memory	−	+	?
Immunity	Innate	Adaptive	Both
Somatic Hypermutation	−	+	+
Markers	CD 5 + CD 43 + CD 23 − CD 19 +	CD5 − CD43 − CD 23 + CD 19 +	CD 5 − CD 43 − CD 23 − CD 19 +
Surface Ig	IgM + (↑) IgD + (↓)	IgM ↑ IgD ↓	IgM + (↑) IgD + (↓)

B-CELL ACTIVATION:

Types:
① T-Cell Dependent
② T-Cell Independent (immediate response)

} T-dependent is more efficient than T independent

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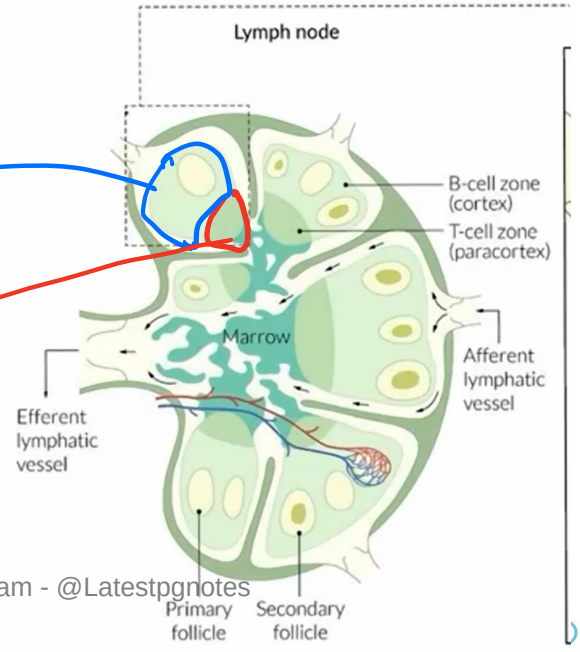
	T-Dependent	T- independent
Property	2° response Complex	1° response Simple
Structure	→ Protein – Glycoprotein – Peptides – Lipoproteins – Protein-nucleoprotein complexes	– Polysaccharide (Imp. for Pneumococcus) – Dextran polyvinyl pyrolidone – Lipopolysaccharide (Gram -ve)
Antibody	– IgG/IgM/IgA ± IgE/IgD } Polyclonal response	– IgM → Polyspecific (Germline Ab)
T cell activation	→ +++ follicular 'T' helper (CD4)	– No
Location	→ Germinal centre (follicular)	– B_1/B_2 marginal zone
Memory	→ +	→ –
Class switch	→ +	→ –
Booster	+	–
Ab production	At birth	3-18 mo

T-DEPENDENT RESPONSE:

→ Occurs in follicles

Cortex (B cells)

Paracortex (T cell prod.)



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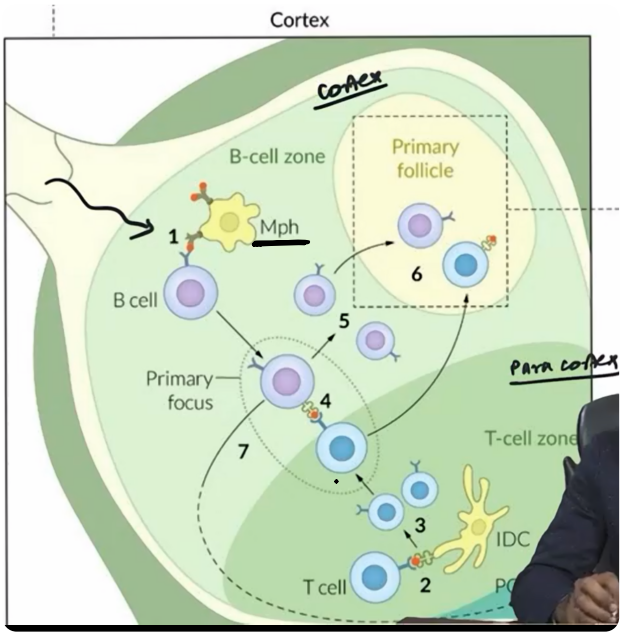
Steps of B cell Activation:



Ag exposure to B cells
↓
APC (Macrophages & DC) gets activated
↓
(i) Macrophages migrate to B cell zone to activate B cells
(ii) DC - migrate to Paracortex to activate T cells
↓
At the junction of cortex & Paracortex, B & T cell interact c̄ each other through MHC II on B cell & TCR on T-cell
↓
CD 40 of B cell interacts c̄ CD 40 ligand on T cell
↓
T cell releases IL-4 which further activates B cell
↓
Activated B cells enter the cortex & from there into the follicles

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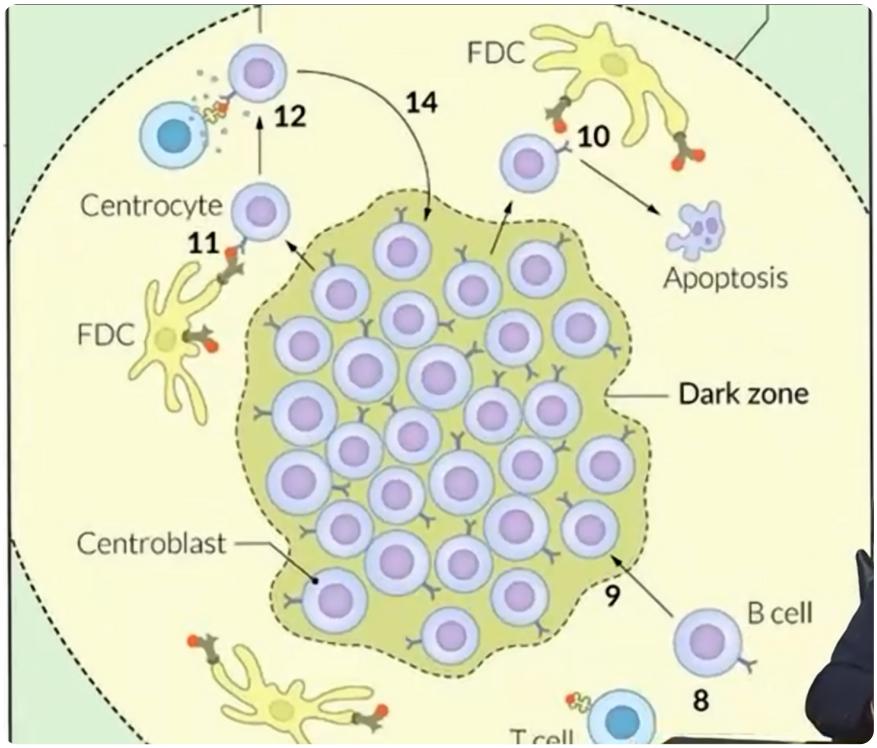


→ Activated B & T cells enter the 1° follicle, cause GC reaction

↓

Remaining inactive B cells are pushed to Mantle zone

→ After the GC reaction, 1° follicle becomes 2° follicle

→ Germinal centre –

a) Dark zone – Centre
b) Light zone – Peripheral

Activated B cell (which received survival signal from 'T' cells)

↓

enters follicle from cortex

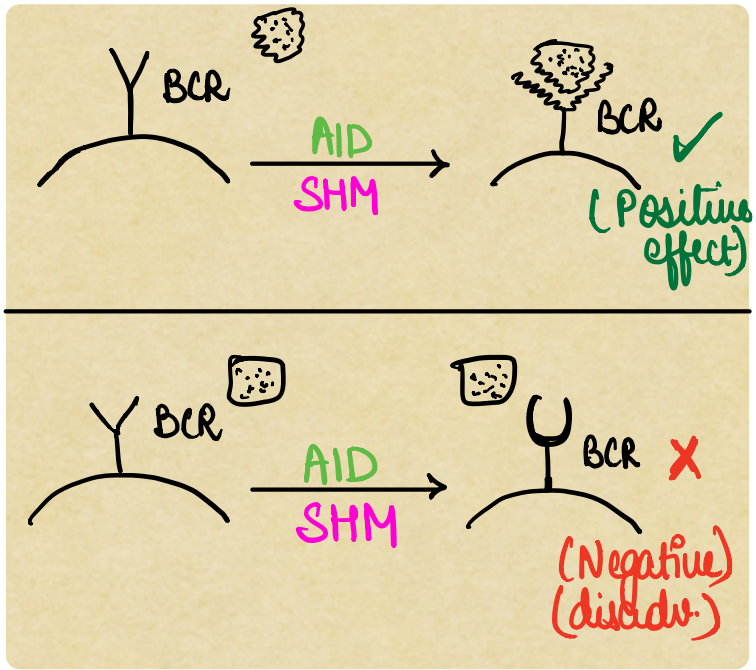
↓

B cells enters the dark zone of Germinal centre & becomes Centroblast

↓

Centroblasts undergo SHM (Somatic Hypermutation) to become super specialised

[SHM is triggered by CD40-CD40L interaction]



[AID – Activation Induced Cytidine Deaminase]

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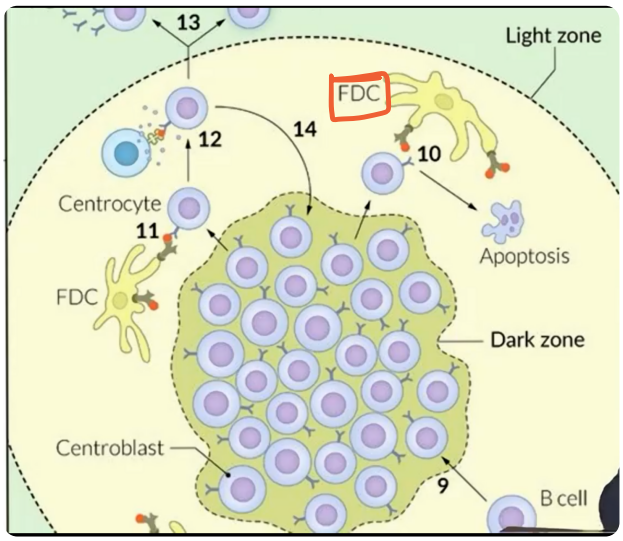

→ FDC – Follicular Dendritic cells
↓
very few & have the same Ag which the B cell was exposed to.

B cells after SHM have either
- positive effect → bind to FDC & survive (light zone of GC) → Survived B cells are called Centrocytes
- negative effect → Apoptosis

↓

Centrocytes again interact c̄ T cell (T helper cell) } If this doesn't occur, B cells die

[MHC II – TCR
CD40 – CD40L] } Interactions

↓

T cells produce Cytokines

depending on the CK produced
- → Plasma cells → migrate → BM
- → Memory cells

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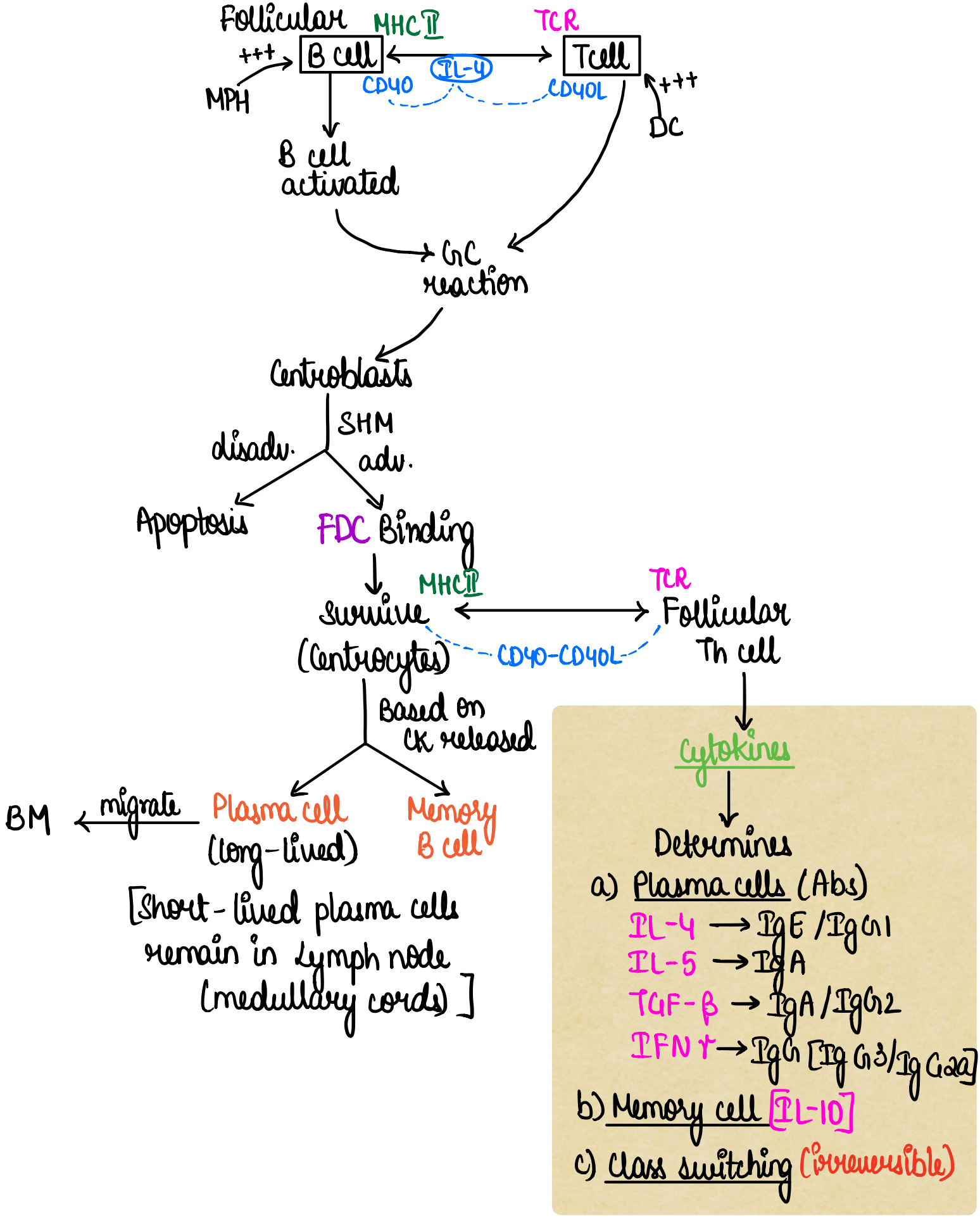

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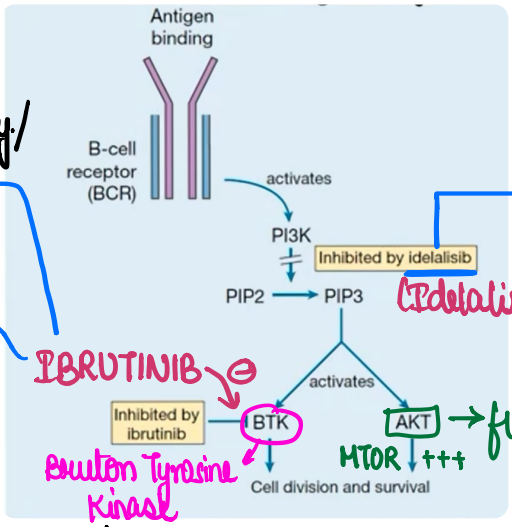
B - cell Basics and beyond

BCR SIGNALLING:

Uses - (Relapse) CLL / Mantle cell ly./ Chronic GVHD

Similar Drugs
Acalabrutinib
Zanabrutinib



IBRUTINIB ⊖

(Idelalisib)

Similar drugs } - Copanalisib, Alpelisib, Duvelisib } used for relapsing lymphomas (eg: CLL)

Bruton Tyrosine Kinase

→ further cell activation & proliferation is by anti-apoptotic gene BCL6

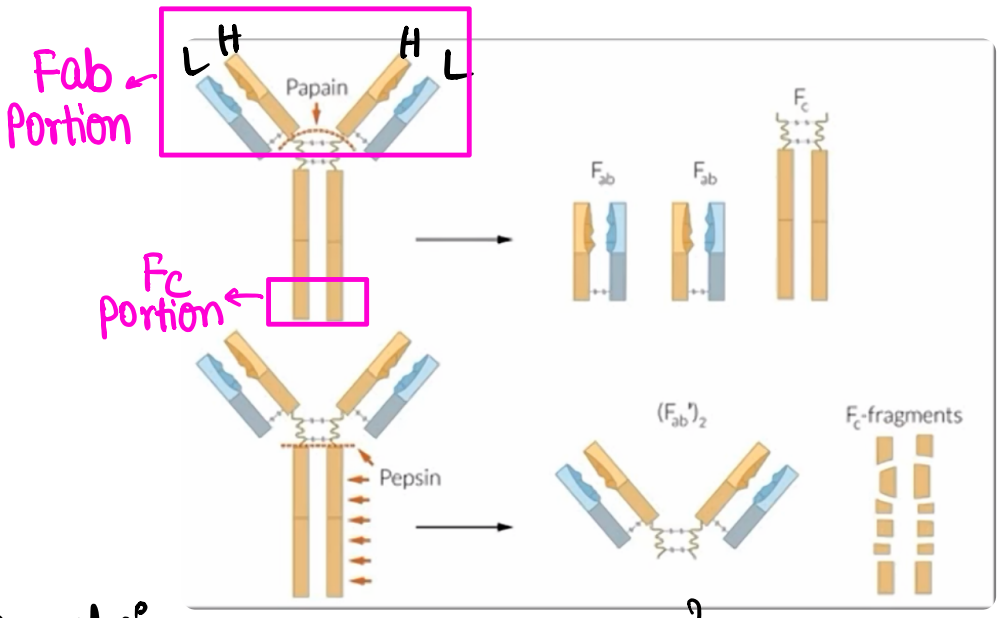
$PIP_2 \xrightarrow[\text{Phospholipase C}]{+++} IP_3 + DAG$

$IP_3 \rightarrow Ca^{+2} \rightarrow NFKB$

$DAG \rightarrow RAS-MAPK$

NFKB, RAS-MAPK → ↑ cell proliferation & survival

IMMUNOGLOBULINS:



→ H - Heavy chain
L - Light chain → can be either κ/λ (but not both)

Overall → 2 H + 2 L chains

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Fab Portion →

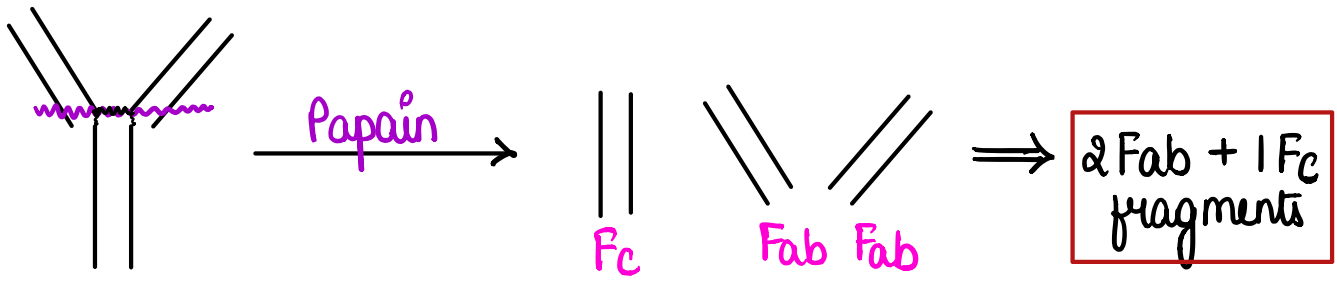
- → made of both H & L chains
- → Ag binding site
- → Contains hypervariable / variable regions
- → specific to a particular idiotype of antibodies (ab) ⇒ single Ag bind.

Fc Portion →

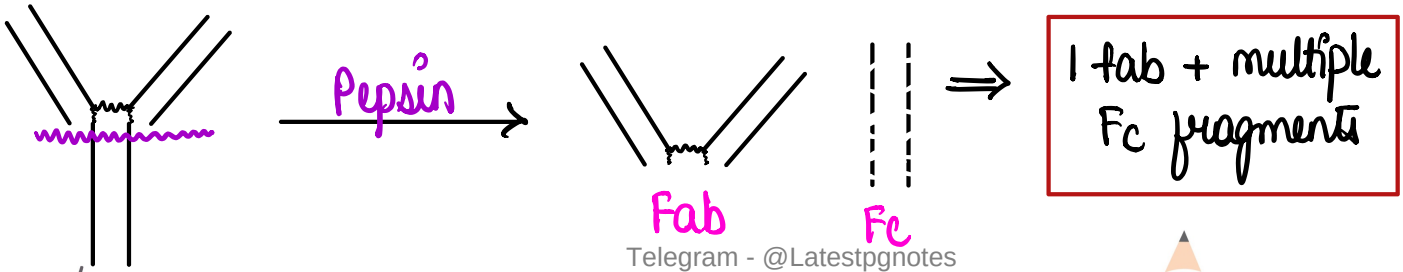
- → made of only Heavy chains
- → It is constant
- → Determines Isotype of Ab → IgG / IgA / IgM / IgE / IgD
- → * Heavy chains determine the type of Ab.
- → Bind to Immunological cells
- → Activates Complement system
- → FcR (Fc Receptors) → Present on Phagocytic Cells & Cytotoxic cells

Cleavage Reaction :

① Papain cleavage –



② Pepsin cleavage –



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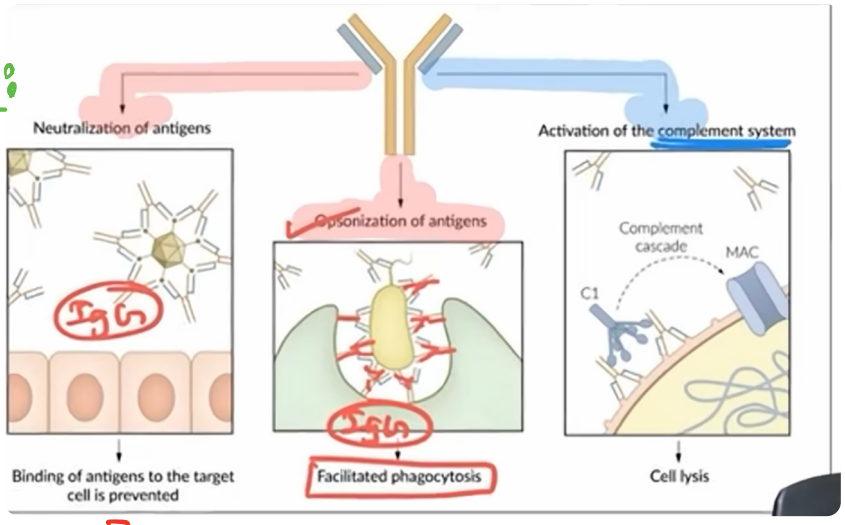
Functions of Ig :

① Neutralisation of Antigens (Ag):

→ Ig binds to Ag & prevents the Ag from binding to target cells. [Best - IgG]



② Opsonisation of Ags:

→ Coats Ags for Phagocytes to recognise them easily [Best - IgG]

③ Activation of Complement System:

→ facilitates cell lysis [Best - IgM > IgG > IgA] ~~IgE~~ ~~IgD~~

do not activate

Specificity

① Ag dependent

② Activity ↑ by SHM (through AID) & Affinity maturation

③ Determines class switching

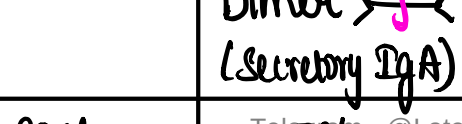
Diversity

① Ag independent

② Determined by genes

③ Heavy chains - V-D-J recombinatn.
Light chains - V-J recombination

④ Action - Random (through Tdt)

	IgM	IgG	IgA	IgE	IgD
H chains	μ	γ	α	ε	δ
Structure	Pentamer	Monomer Y	Y Monomer/ (Blood circ.) Dimer (Secretory IgA) 	Monomer Y	Monomer Y
Serum conc	5%	80%	15%	0.002%	1%

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	IgM	IgG	IgA	IgE	IgD
t1/2	5-6 d	21 d (max)	5-6 days	3 days	3 days
Cross placenta	–	+++	–	–	–
Fc binding	–	+++ (Phagocytes	–	++ Mast cells Basophils	–
Complement fixation	+++++	+++	+/–	–	–
Function	- Primary response - helpful in early Δ - Best complement fixation - can't cross vascular comp. - Surface IgM (BCR) is monomeric Y SIgM Bcell	2° response - States Past/ Chronic infection - long term immunity - Best opsonise & neutraliser	- mucosal immunity	- allergic response (T1 HSR)	- SIgD ↓ BCR (esp. of follicular B cells)

* m/c Ab in blood – IgG
* 2nd m/c Ab in blood – IgA
* max. secreted Ab by the body – IgA
* IgA → Secretory IgA has a secretory component which is added by the stomach (through post translational modification) to survive the acidic medium.

* IgG → IgG1 → Best Phagocyte binding
  IgG2 → Poorly crosses placenta
  IgG3 → 1st Ig to come into blood as an immunological response
  IgG4 →

t1/2 – 7d ← IgG3

→ Best compliment activator

among IgG subtypes

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IMMUNOLOGICAL MEMORY :

Memory

Memory B cells

Centroblasts → Centrocytes

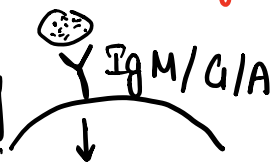
+++ ← T cell signal

- Plasma cells
- Memory B cells

[CD 45 RO – marker of memory cells]

(sustained binding of CD40-40L ; IL-10 are needed for this)

↑↑ affinity (to that particular Ag already exposed in the past)



↓

→ direct Plasma cells formed

↓

Ab.

Memory T cells

Effector memory T cell

↓

- circulation
- peripheral tissues
- CCR7 –
- CD4 +
- C3 +

Central memory T cell

↓

- 2° lymphoid organs
- CCR7 +
  (holds the T cells in LN)

CONGENITAL IMMUNODEFICIENCIES :

B cell

1. Bruton Agammaglobulinemia
2. Selective IgA def.
3. Common Variable Immuno Def. (CVID)

T-cell

1. Di George Synd.
2. Hyper IgE / Job synd.
3. IL-12 γ def.
4. APECED (Type I APS)
5. Immuno Polyendocrinopathy X-linked (IPEX)

B + T cells

1. SCID
2. Wiskott-Aldrich
3. Hyper IgM synd.
4. Ataxia telangiectasia

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B-CELL DISORDERS:

① Bruton's Agammaglobulinemia:

→ X-linked recessive (♂)
→ deficiency of Bruton Tyrosine Kinase
→ ↓ mature B cells
→ Manifest at >4-6 months age

C/f - ① Pyogenic infections (encapsulated organisms)
② Hypoplasia of lymphoid tissue

Δ - ① ↓/absent B cells
② Ⓝ T cell count
③ ↓ Ig (all)

* no lymphadenopathy

② Selective IgA deficiency:

→ m/c 1° immuno deficiency synd.
→ unknown mechanism

C/f - ① Asymptomatic (m/c)
② Symptomatic → mucosal infections
chronic diarrhoea
Recurrent Pneumonia
Candidiasis (rare)

③ ↑ risk of a) Gluten Hypersensitivity [Coeliac dis]
b) IBD
c) Atopy

Δ: ↓ Sr. IgA ; Other Ig - Ⓝ

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③ Common Variable Immuno Deficiency :

→ B cells are not converted to Plasma cells.

→ ↓ Igs of all classes

→ Onset – 20-35 yrs

C/f –

① Sinopulmonary infections

② ↑ lymphomas

③ Auto immune disorders

④ Bronchiectasis

⑤ Poor response to Immunizations in a Normally growing child

Δ :

Ⓝ B/T cells

↓ Plasma cells

↓ Igs

T-CELL DISORDERS :

① DiGeorge Syndrome :

'CATCH 22'

C – Cardiac anomalies

A – Anomalous face

T – Thymic aplasia

C – Cleft palate

H – Hypocalcemia

22 – Chr 22 defect (22q 11.2) → determines 3rd/4th Pharyngeal arches ↓ Thymus / PTH glands

Δ –

① CXR – Absent thymic shadow

② ↓ PTH / ↓ Ca^{+2}

③ ↓↓ T cells

→ No Cell Mediated Immunity / Delayed Hypersensitivity

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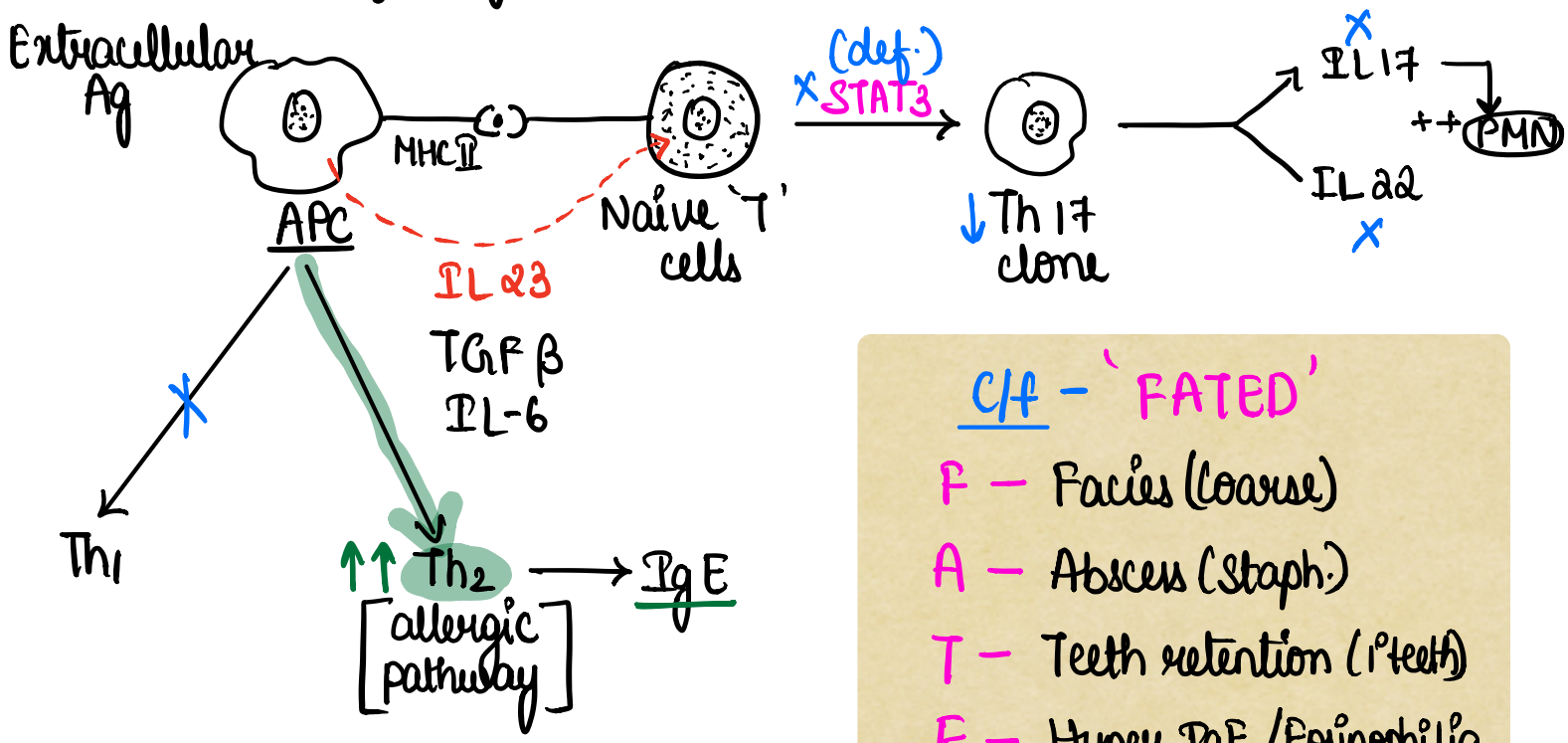
② Hyper IgE Syndrome :

→ Job syndrome [AD]

→ STAT 3 deficiency



Δ - ↑↑ IgE / Eosinophilia

C/f - 'FATED'

F – Facies (Coarse)

A – Abscess (Staph.)

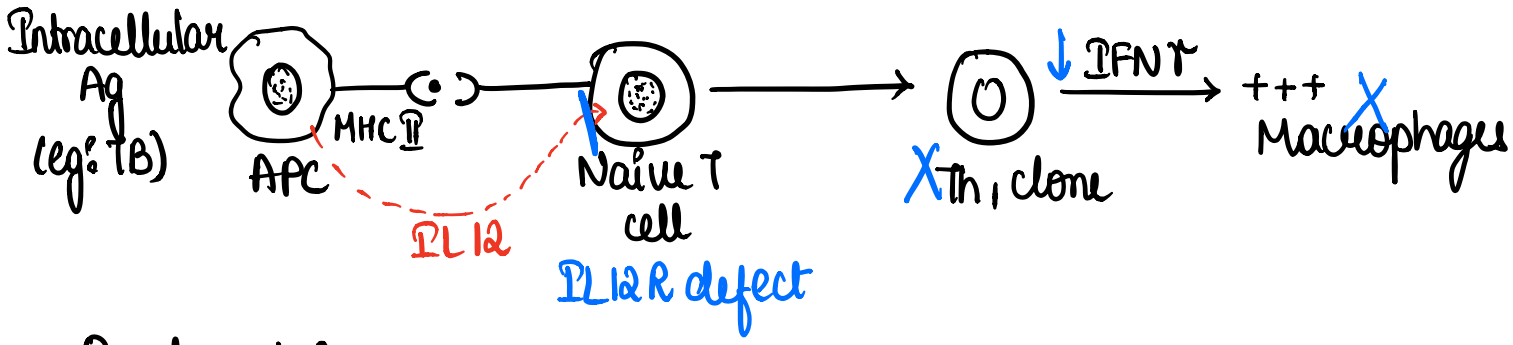
T – Teeth retention (1° teeth)

E – Hyper IgE / Eosinophilia

D – Dermatological

③ IL-12 R Deficiency :

→ [AR]



→ Onset – 1-3yrs

→ Examples – Disseminated TB
Fungal infections

→ ↓ IFN γ

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B + T - CELL DISORDERS :

① Severe Combined Immuno Deficiency :

Types -
① X-linked recessive → IL 2R deficiency
② AR → Adenosine Deaminase deficiency

C/f - Asymptomatic @ Birth
- ↑ risk of Bacterial / viral / fungal / Protozoal infections
- Chronic diarrhoea
- failure to thrive
- Absent L.N / tonsils

Bubble Boy

Δ - ① (Quantitative) PCR :
↓ TRECs [T-cell Excision Circles]
② Absent T cells (XLR type)
③ Absent T / B / NK cells (AR type)
④ Absent thymic shadow
⑤ LN Biopsy : Absent Germinal Centres

② Wiskott Aldrich Syndrome :

→ X-linked recessive [♂]
→ WASP gene mutation → ↓ Ag presentation
↓
↓ T cell function
(↓ B cell " also)

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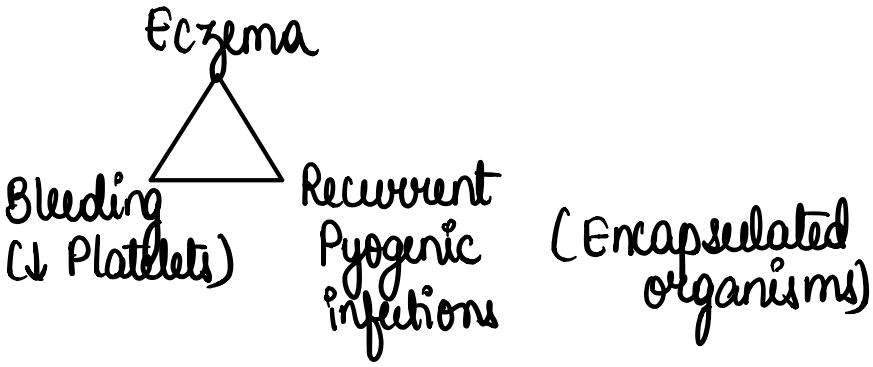
C/f -

① Onset - @ Birth

②



Δ :

↓ IgG / IgM

↑ IgE / IgA

↓ Platelets c̄ Small Platelets

Genetic analysis - for WASP gene mutation

③ Hyper IgM Syndrome :

→ X-linked Recessive [♂]

Centrocytes ⟷ T cells ✗

CD 40 - 40L ✗

↓

✗ Isotype switching [IgM ↑↑↑ ⟶ IgG]

C/f - ① Recurrent Sinopulmonary infections [failure to thrive]

② Recurrent infections c̄ PCP / Histoplasma / CMV / Cryptosporidium

③ ↑ IgM + ↓ IgG / ↓ IgA / ↓ IgE

④ Flow cytometry - CD40L deficiency

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④ Ataxia Telangiectasia :

→ [AR]

→ ATM gene ✗ (mutation) ⟶ repairs ds DNA breaks ✗ ⟶ ↑↑ ds DNA breaks
⇓
↑ cell cycle arrest

C/f – 3 'As'

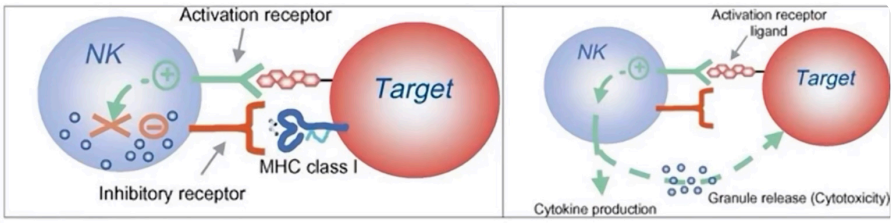
① Progressive Ataxia (d/t Cerebellar atrophy)
② Spider Angiomas
③ IgA deficiency ⟶ ↑ infections
Sinusitis
Pneumonia
Ear infections
Diarrhoea

→ ↑↑ sensitivity to Radiation ⟹ ↑↑ radiation related damage
↑↑ malignancy [also seen in Wiskott Aldrich Synd.]
↳ leukemias / lymphomas

Δ – ① MRI → cerebellar atrophy
② ↑ AFP levels
③ ↓ IgA / IgG / IgE
④ Lymphopenia

NK Cell

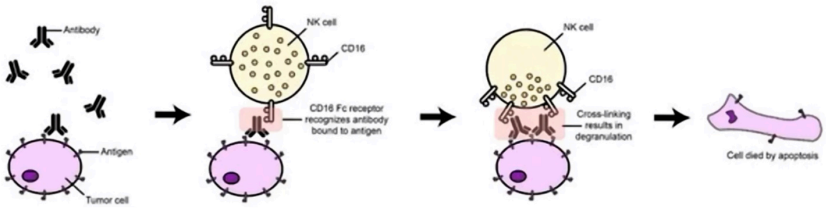
NK CELL :



Origin of NK Cell :

→ originates from lymphoid precursors

Markers : CD16/56



Mechanism Of Action :

① ↓ MHC I expression on cells → cells ∄ MHC I become target for NK cells

② Ab dependent Cell Mediated Cytotoxicity (ADCC)
③ Cytokine production

} Mechanisms of Killing by NK cell

Receptors :

Target Cell	NK Cell	Effect
① MHC I (inhibiting)	Kir	Inhibiting
② MIC-A (Activating)	NKG2D / Ly49H	Activating

* If NK cell has both activating & inhibiting receptors, nothing happens
* If there is no MHC I → NK cell gets activated } → release of granules
↓
Cytokine production (TNFα / IFNγ) → Kills Target Cell

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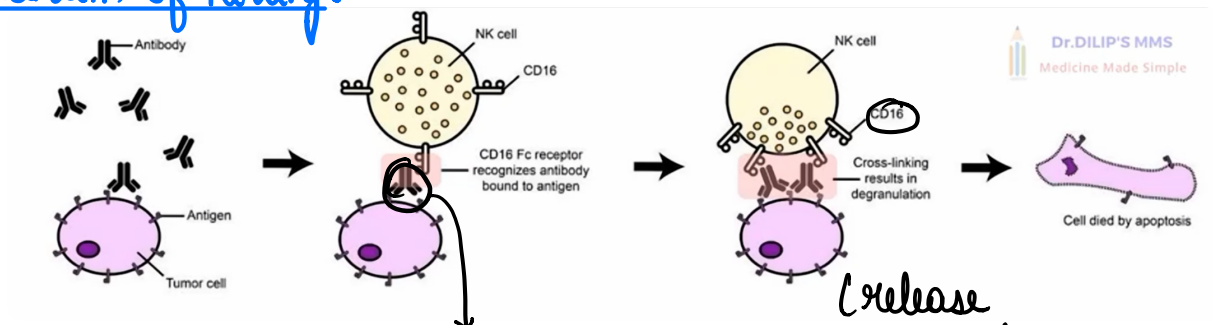
→ IFN γ → Vasodilator

TNF α → recruits neutrophils, macrophages → ⊕ Phagocytosis

Activating receptor	Inhibiting receptor	Effect
+	−	Kill
−	+	No effect
+	+	No effect
−	−	No effect

Mechanism of Killing:



(release of granules & cytokines)

Opsonisation (IgG)
[coated c̄ Antibodies]
⇓
Cells are recognized by CD16 (FC γ Receptor)
⇓
Granules released from NK cells & also cytokines are produced } ⇒ Kill the target cell

Cytokine Production → IFN α / IFN β, IL-2 / IL-12 } ⇒ ↑↑ NK cell activity

± IFN α / IFN γ

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Basics of Lymphoma

	Lymphoma	Leukemia
① Malignant cells –	Nodes ± 2° lymph organs	Blood Bone Marrow
② Includes –	ALL SLL	ALL CLL

HL (vs) NHL :

	HODGKIN LYMPHOMA	NON-HODGKIN LYMPHOMA
① Origin	B cell	B cell (85%) / T cell (15%)
② RS cell	+++	– –
③ Age	≃ 30yrs	≃ 60yrs
④ Lymph nodes [Firm, Rubbery] [Non-tender] (Tender nodes point towards infection)	– Supra-diaphragmatic (m/c) Cervical > Supraclavicular + Mediastinal	– Supra + Infra diaphragmatic m/c – Cervical
	– Contiguous	– non-contiguous
	– Nodal disease only	– Nodal + (Extranodal) (m/c – BM >> GIT)
	– No involvement of Waldeyer's & Mesenteric nodes	– They can be involvement
⑤ Lungs	– 10%	– 30%
⑥ Rx	– ABVD ± RT	– R-CHOP ± Mtx (if CNS)
⑦ Prognosis	– Excellent (Based on anatomical staging)	– Variable (not based on anatomical staging)
⑧ B symptoms (indicates poor prog)	– 35%	– 15-50%

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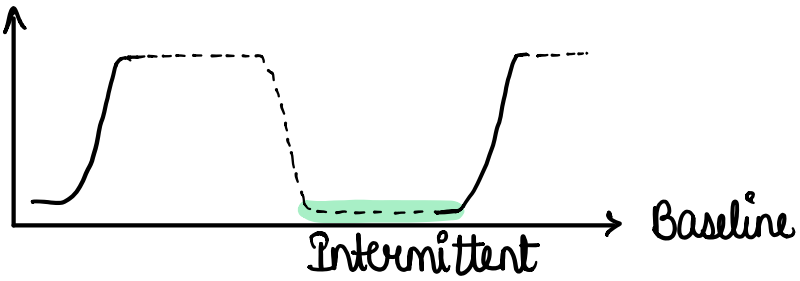
'B' Symptoms – Fever (>38°C) (Pel Ebstein fever)
Night Sweats
Wt. loss (>10% in 6 months)

Pel-Ebstein Fever: (seen in HL) → recurrent fever



DIAGNOSIS:

① **Excisional Biopsy** (or Trucut): Sent for HPE
(Preferred)
IHC
Cytogenetics

② **BM Biopsy** – to look for Extranodal involvement

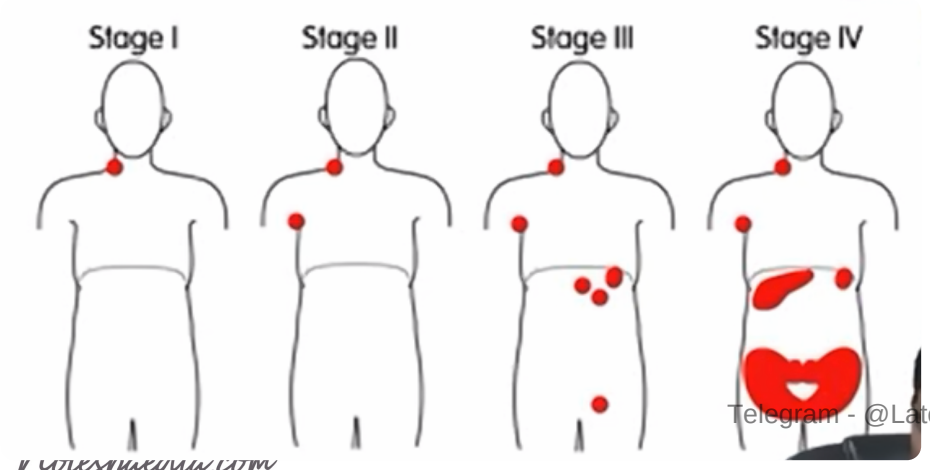
③ **LP (CSF)** – If there is CNS involvement

④ **PET** – for Anatomical Staging (Preferred over CT) [PET >> CT]

STAGING:

ANN-ARBOR STAGING (E COTSWALDS MODEL)

Others – ① Lugand
② TNM Paris [1° GI NHL]



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Stage 1 – Single LN/lesion

Stage 2 – ≥2 LN regions on same side of diaphragm [Supra > Infra]

Stage 3 – Both sides of diaphragm

Stage 4 – Disseminated [LN involvement is optional]

- any extranodal involvement (eg: Bone Marrow)
- Spleen involvement → HL – nodal
  NHL – Extranodal
- Lymph node, Thymus, Waldeyer's ring } Nodal ⇒ Anything other than this is extranodal

Subclassification for above Stages:

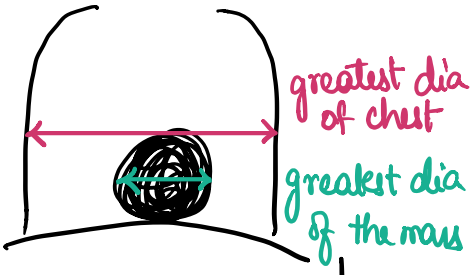
A – no Symptoms

B – B Symptoms

X – Bulky dis. (Mediastinal mass)

↓ if infra diaphragmatic (abdomen)

↓ diameter of mass > 10 cm



↓ { if > 1/3 of transverse diameter of the chest wall

E – Single Contiguous Extranodal Site

H – Hepatic involvement

S – Splenic involvement

CLASSIFICATION OF NHL:

NHL
- B-Cell (85%) (mature)
- T-Cell (15%) (mature)

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① B-cell NHL :

1. Burkitt lymphoma (most aggressive among the mature B cell NHL)
2. Diffuse large B-Cell Lymphoma (DLBCL)
3. Mantle Cell Lymphoma
4. Marginal Zone Lymphoma
5. Hairy Cell Leukemia
6. Follicular lymphoma } mostly indolent
7. CLL / SLL

Aggressiveness

② T- Cell NHL :

① Cutaneous

a) 1° Cutaneous lymphoma (CD 30+)
b) Mycosis fungoides (leukemic cells in skin only)
c) Sezary syndrome (leukemic cells in skin & blood also)

② Extranodal :

a) NK / T cell (Nasal type)
b) Enteropathy associated TCL
c) Hypersplenic TCL
d) Subcutaneous Panniculitis like TCL

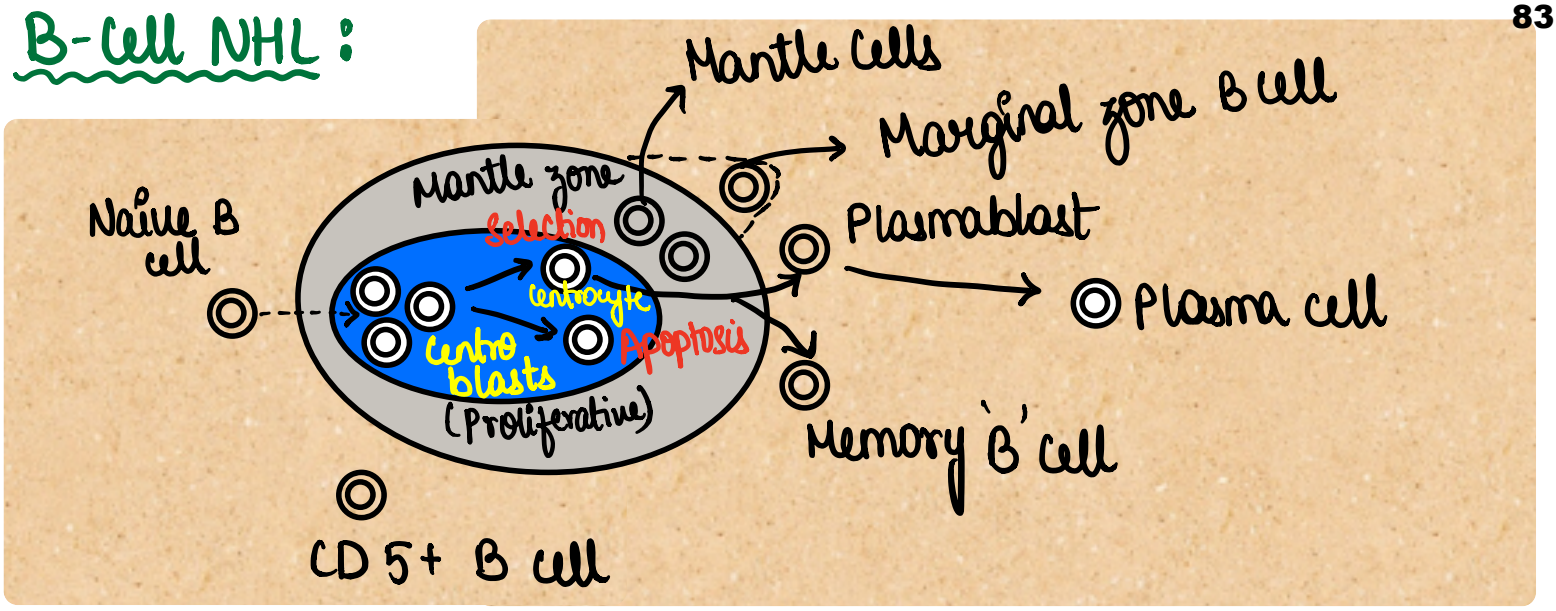
③ Nodal :

a) Peripheral TCL (Not Otherwise specified - NOS)
b) Anaplastic Large cell Lymphoma (ALCL)
c) Angioimmunoblastic TCL

④ Leukemic :

a) Adult TCL / Leukemia (ATCL)
b) Aggressive NK cell Leukemia
c) T cell Prolymphatic Leuk.
d) Large Granular Lymphocytic leukemia (LGL Leuk.)

B-Cell NHL :



* <u>Marginal Zone 'B' cells</u> – Physiologically seen only in spleen
  – When they turn malignant → they come into blood & deposit in nodes → Nodal Marginal Lymphoma

Cell	Type of NHL
① Mantle cells →	① Mantle Cell Lymphoma
② CD5+ 'B' cell →	① CLL (unmutated)
③ Centroblasts →	① DLBCL (GCB-Germinal Centre B cell lymphoma)
	② 1° Mediastinal 'B' cell lymphoma } very aggressive
	③ Burkitt's lymphoma } very aggressive
	④ PTLD } less aggressive (or) more indolent
	⑤ Follicular lymphoma } less aggressive (or) more indolent
④ Centrocyte →	① Nodular Lymphocyte Predominant HL
⑤ Apoptotic cell →	① Classic HL
⑥ Plasma Blast →	① DLBCL (Activated B cell Phenotype - ABC)
	② 1° Effusion Lymphoma
	③ Lymphoplasmacytoid lymphoma
⑦ Plasma cell →	① Multiple Myeloma

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→ Malignant Plasma cells ⟶ Migrate to BM ⟶ So, Multiple Myeloma is a neoplasm of Bone Marrow

⑧ Memory B cell ⟶
① CLL (mutated)
② Hairy cell leukemia
③ 'B' cell Prolymphocytic leukemia

HPE of NHL:

Classification of NHL based on Morphology (depending on HPE findings):

NHL

Homogenous

① Small cell –
a) SLL/CLL
b) Mantle cell
c) Follicular ly.
d) Marginal zone ly.
e) Peripheral T cell ly.

② Medium cell –
a) Burkitt lymphoma
b) NK/T cell ly.

③ Large cell –
a) DLBCL
b) Plasmoblastic ly.

Heterogenous

① Mainly small –
a) Reactive hyperplasia of LN
b) Follicular Ly.
c) Marginal zone ly.
d) SLL/CLL
e) Peripheral 'T' cell ly.

② Mainly large –
a) Reactive (Immunoblastic) lymphoma.

⟷ Classic HL

Pleomorphic

① Anaplastic Large Cell Lymphoma (ALCL)

⟷ Lymphocyte Depleted HL

* We can't confirm/manage NHL based on HPE. We should go for IHC & cytogenetics

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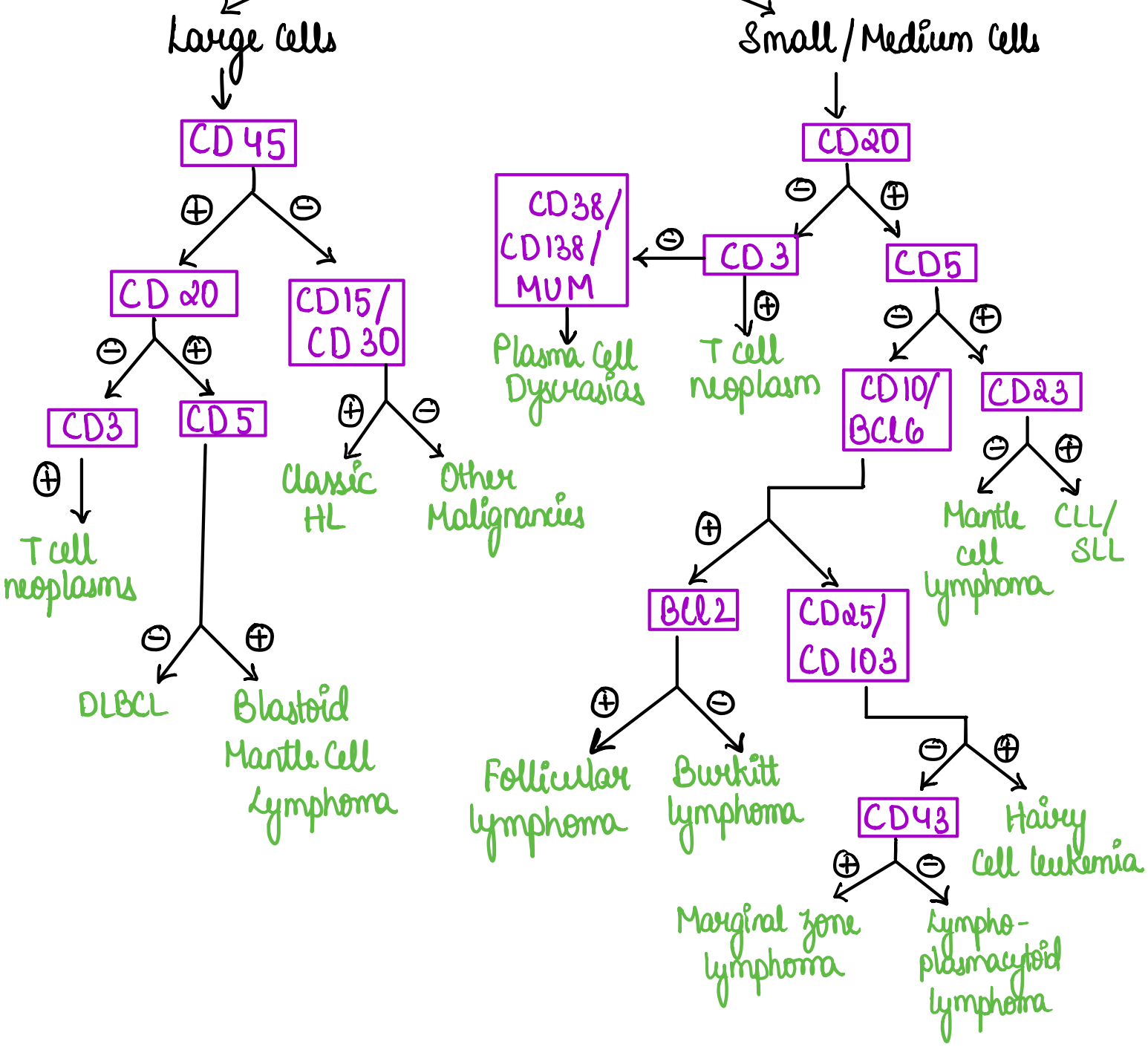
Suspected Lymphoma



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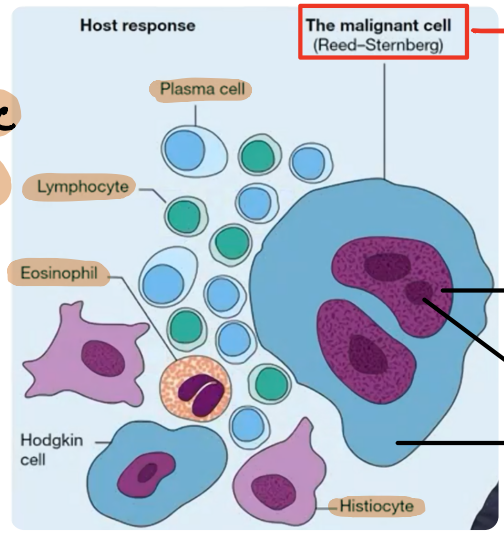
Hodgkin's lymphoma

REED-STERNBERG CELL:



→ <1%

Non-neoplastic inflammatory cells

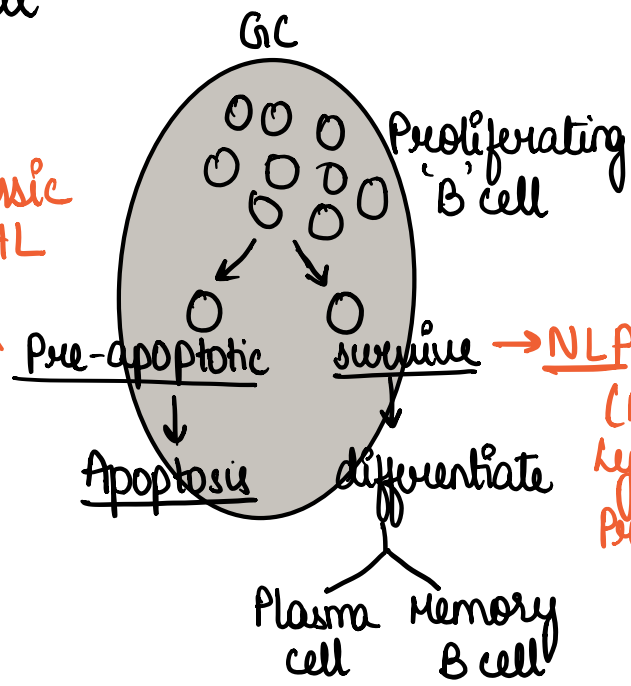
→ Bilobed nucleus
→ Nucleoli
→ Clear cytoplasm

} Owl's eye appearance

Origin – Germinal centre 'B' cell [PAX5+/ BSAP+]

Crippled B cell ← (RS cell)

Classic HL



→ NLP HL (Nodular Lymphocytic Predom.)

→ 'Popcorn' type of lymphohistiocytes

Other types of RS cell:

1. Mononuclear RS
2. Lacunar RS

R-S like Syndromes →

1. 1° Mediastinal 'B' cell lymphoma
2. Angioimmunoblastic 'T' lymphoma
3. EBV associated mucocutaneous ulcers

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HODGKIN'S LYMPHOMA:

Epidemiology – Age ≃ 30yrs ; M > F [♂ : ♀ = 2:1]

↓

Bimodal

15-35yrs ; >50yrs

Risk factors – ① EBV
② HIV

C/f –

① Lymphadenopathy → Superficial [cervical/axillary] (m/c)
(Painless/non-tender)
[Pain ↑ c̄ alcohol in 10-15% cases]
– Supradiaphragmatic
⇓
No Waldeyer's ring
No Mesenteric nodes

② Hepatosplenomegaly – rare

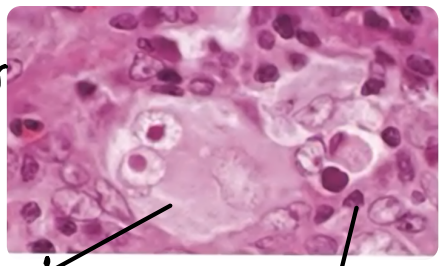
③ Mediastinal involvement – rare [<10%]

④ 'B' symptoms → presence indicates poor prognosis

⑤ Pruritis (10-15%)

Types:

① Classic HL (95%)

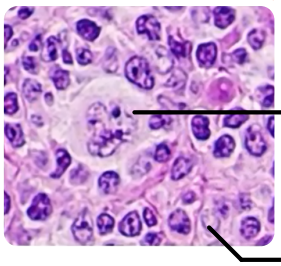


Tumour cells

RS cell (classic)

Inflammatory infiltrate (Pleomorphic)
[Plasma cells/ lympho/histiocytes/ Eosinophils]

② Nodular lymphocyte Predom. (NLP) (5%) – rare



→ Popcorn cell (Lymphohistiocytes)

→ Inflammatory [lymphocytes + histiocytes]
B>T

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	CLASSIC HL	NLP
① CD markers	→ CD 15/30 + CD 45 − CD 19/20 − EMA − BCl6 − [<10% +] J chain − CD 79a (variable / −ve)	→ CD 15/30 − CD 45 + CD 19/20 + EMA + BCl6 + J chain + CD 79a +
② EBV association	common (≃ 50%)	⊖
③ Architecture	− no follicular dendritic cell meshwork	− follicular DC meshwork
④ 'B' cells	− Crippled / Pre-apoptotic [S.Ig − / S.H −]	− Selected B cells [S.Ig + / S.H +]
⑤ Prognosis	− Variable	− Excellent

Rx of HL:

Stage I/II

ABVD ± RT (if Bulky)
↓
2-4 cycles

A - Adriamycin
B - Bleomycin
V - Vinblastin
D - Dacarbazine

Stage III/IV

ABVD ± RT (if Bulky)
↓
6-8 cycles

→ If PET becomes '−ve' after first 2 cycles, we can omit Bleomycin in subsequent cycles

→ Bleomycin can be replaced by Brentuzumab vedotin [anti CD30] (↑ toxicity ↑ effective)

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BEACOPP regimen – for Stage III / IV

B – Bleomycin
E – Etoposide
A – Adriamycin (Doxorubicin)
C – Cyclophosphomide
O – Oncovin (Vincristine)
P – Prednisolone
P – Procarbazine

Relapse →

① Salvage chemo + autologous HSCT ± RT

② Brentuximab [in Post HSCT cases]

③ PD1 / PDL1 ⊖ → Pembrolizumab
Nivolumab

Rx of NLP :

→ Similar to classic HL
→ But Brentuximab is not used
→ Rituximab is used [Rituximab can't be used in classic HL]

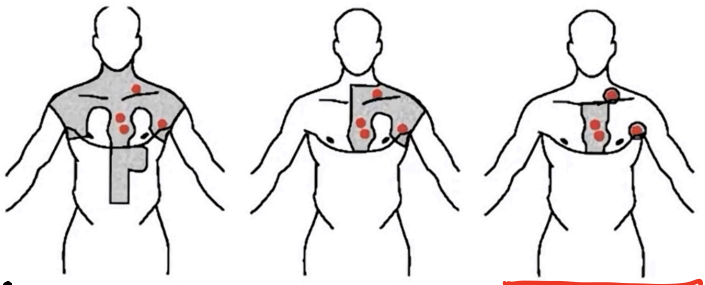
Refractory / Relapse :

① Salvage Chemo ± Rituximab ± Autologous HSCT ± RT

② MOPP regimen –

M – Mechlory Ethamine
O – Oncovin
P – Procarbazine
P – Prednisolone

RT :



total nodal irradiation { Mantle field RT + Inverted Y RT (not preferred)

Involved field RT

Involved site RT (preferred)

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Late effects of HL:

① **Second cancers** – 4·6 times upto 40 yrs age
- Breast (RT)
- Lung
- AML / MDL / NHL

② **Cardiac disease** –
- dilated cardiomyopathy (d/t Doxorubicin → irreversible)
- Restrictive / constrictive Pericarditis (d/t RT)

③ **Pulmonary Toxicity** – d/t Bleomycin

④ **↓ T_4 [Hypothyroidism]** – ↑ risk of Papillary Ca. of Thyroid

TYPES OF CLASSIC HL:

	NODULAR SCLEROSING	MIXED CELLULARITY	LYMPHOCYTE RICH	LYMPHOCYTE DEPLETED
① Incidence	– 60-80% (m/c)	– 15-30%	5%	<1%
② Gender	– ♂ = ♀	– ♂ > ♀	♂ > ♀	♂ > ♀
③ Clinical features	– Young adults – frequent mediastinal lymphadenopathy – Stage I/II @ Δ – Lacunar RS – Collagen Bands	– Older – EBV ⇒ 70% – 50% @ stage III/IV – Pleomorphic	– no mediastinal lymphadenopathy – EBV – 40% – lymphocytes +++ – distortion of LN architecture	– older – diffuse fibrosis – large no. of RS cells – HIV (max. ass.)
④ Prognosis	Good	Intermediate	Good	Worst

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KEY POINTS :

Best Prognosis → NLP > NS ≥ LR

Worst Prognosis → LD

m/c → classic (N.S)

Max EBV → Mixed cellularity

Max HIV → LD

Average cure rate → 85%

NS – nodular sclerosis

NLP – Nodular lymphocyte predom.

LR – Lymphocyte Rich

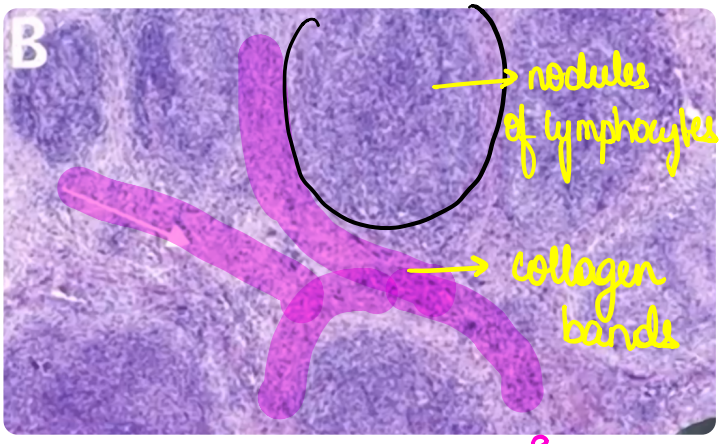
INTERNATIONAL PROGNOSTIC SCORES :

'–ve' Prognostic factors →

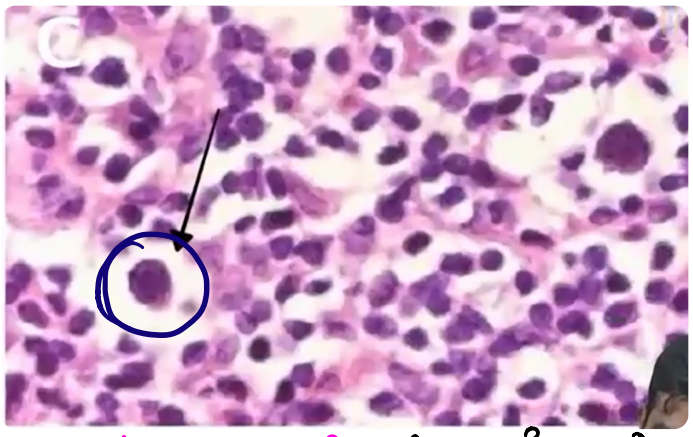
1. Age > 45 yrs — 1
2. Hb < 10.5 g% — 1
3. Males — 1
4. Albumin < 4 g% — 1
5. Stage IV — 1
6. WBC < 15,000 — 1
7. Lymphocytes < 600 (< 8%) — 1

> 3 ⇒ BEACOPP regimen

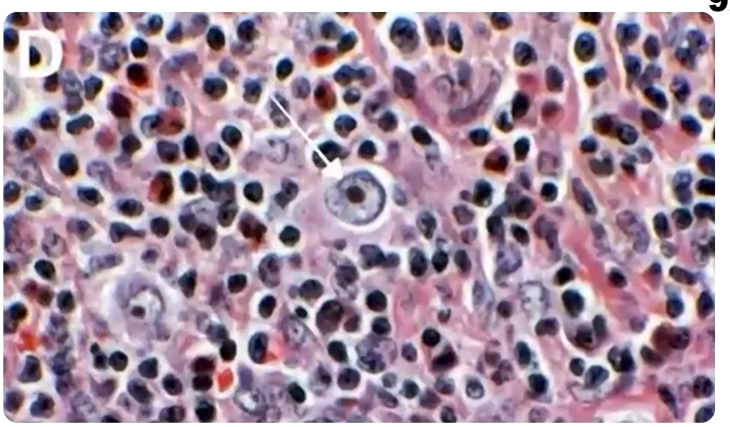
Classic HL



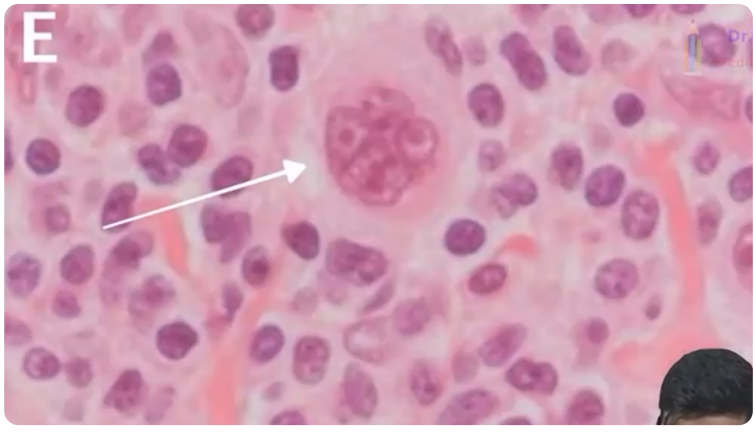
Nodular Sclerosis



Lacunar RS (seen in NS)



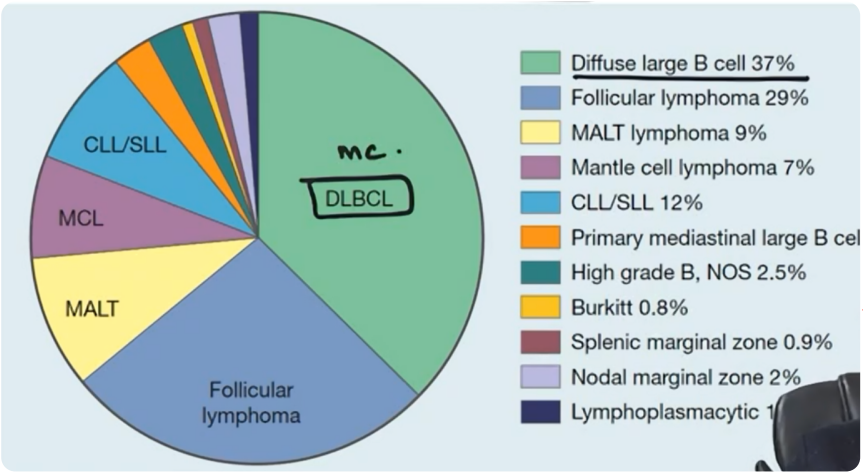
Mononuclear RS cell



Multinucleated RS cell

Mummified / Pyknotic RS cell

Non - Hodgkin's Lymphomas



→ B - Cell NHLs → 85%
→ most aggressive NHL → Burkitt's lymphoma
→ most indolent NHL → CLL/SLL
→ m/c NHL → DLBCL
→ 2nd m.c → follicular lymphoma

CLASSIFICATION :

Cell type	Examples	Cytogenetics	Gene mutations
Mature 'B' cell	① Burkitt's lymphoma	t(8;14) / t(2;8) / t(8;22) [Chr. 8 - myc amplification]	various
	② DLBCL a) Germinal centre B cell b) Activated B cell type	 → t(14;18) → t(3;14)	 → CREBBP/EZH1/myc → CREBBP/NFkB++ (Plasma cell survival needs NFkB)
	③ Mantle cell lymphoma	t(11;14)	→ BCL-1 - IgH (↑ Cyclin D1)
	④ Marginal zone lymphoma	t(11;18) / t(1;14); t(14;18)	→ AP12 - MALT-1 & BCL 10 - Ig ± NFKB enhancement
	⑤ Hairy cell leukemia (TRAP +ve)	non-specific	→ IgH - Bcl2, MLL2
	⑥ Follicular lymphoma	t(14;18)	→ BRAFV600F (≈99%)
	⑦ CLL/SLL	del 13p / del 11q / del 17p / Trisomy 12	→ IgVH / ZAP70 / TP53 / (m/c) SF3B1 / ATM

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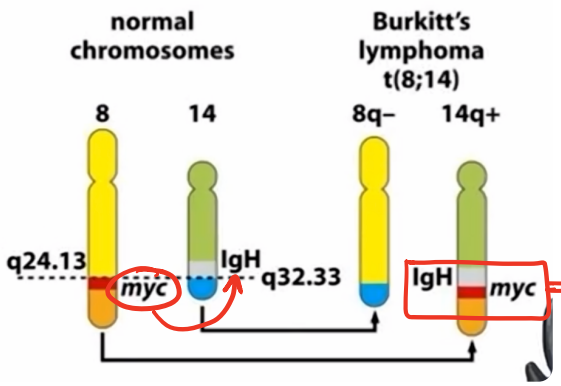
Chromosomal translocations in Burkitt's lymphomas



myc is a proto oncogene

⟹ myc amplification
↓
↑ cell proliferation

Cell type	Examples	Cytogenetics	Gene mutations
Mature T/ NK cell	① Peripheral T cell lymphoma	non-specific	TET2/DNMT3A
	② Mycosis fungoides/ Sezary synd.	–	–
	③ ALCL (Anaplastic large cell lymphoma)	ALK +	
	④ Angioimmunoblastic lymphoma	–	–

ETIOLOGY :

① Infections –

a) Viral → ① EBV – HL/PTLD (Post transplant Lymphoproliferative Disease)
– Burkitt's lymphoma

② HHV 8 – Primary Effusion lymphoma
– Multicentric Castleman disease
– Kaposi Sarcoma

③ HTLV1 – Adult T-cell Lymphoma (ATL)

④ HCV – Marginal zone Lymphoma (MZL)

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② Bacterial – ① H. Pylori – Gastric MALToma
② Borrelia – Cutaneous MALToma
③ C. jejuni – Small Intestine MALToma
④ Chlamydia psittaci – Orbital adnexal MALToma
⑤ Chlamydia pseudomonas – Lung MALToma
– Sezary Synd.

③ Parasitic – ① P. falciparum – Burkitt's lymphoma (esp. Endemic type)

'B' CELL LYMPHOMAS :

I INDOLENT :

① Hairy Cell Leukemia :

→ common in ♂ (middle-aged)

C/f : ① Cytopenia + Massive Splenomegaly + No Lymphadenopathy
↓
20% leukocytosis

Δ : ① PS – 'Hairy Cells' → cells c̄ irregular cytoplasmic projections
② BM – 'Fried egg cells' (non-specific) [Dry tap on BM aspiration → Trephine BM Bx

Markers –
① TRAP +
② CD 103 +
③ CD 11C +
↕ >99% BRAF V006 mutation

② Follicular Lymphoma :

→ 2nd m/c NHL

→ (m/c indolent type of NHL)

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→ Slow progressive / painless Lymphadenopathy [waxing/waning]
→ + Splenomegaly (Stage III / IV @ Δ)
→ ≥ 90% – t(14;18) → IgH ↔ BCL2 ↑↑ (anti-apoptotic)

Markers – CD5 –
CD10 + (GC marker – CALLA)
CD20 +
BCL2 + ↕ BCL6 +

Δ : ① PS – Butt / Buttock Cells (cleaved lymphocytes)

Scoring : Follicular Lymphoma International Index

③ Marginal Zone Lymphoma :

	Splenic MZL (SMZL)	Nodal MZL (NMZL)	MALT
Presentation	→ Splenomegaly	→ Lymphadenopathy	→ depends on site m/c site – Stomach
IgG	+	+	+
IgD	+	+/–	–
CD19/20/79a	+	+	+
*CD5	–	–	–
*CD23	–	–	–
CD10/BCL6	–	–	–
Cyclin D_1	–	–	–

* CD5 & CD23 are done to rule out CLL & Mantle cell lymphoma
CLL → CD5 + CD23 + Mantle cell lymphoma – CD5 + CD23 –

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* Marginal Zone Lymphoma → CD43+ (Specific)
[Majority of MZL will have this +ve]

→ MALT → may be a/w Gastric MALToma → a/w H.Pylori
⇓
Rx – Eradication of H.Pylori

→ SMZL → shows Villous Lymphocytes

II AGGRESSIVE :

① Burkitt's Lymphoma :

Types –

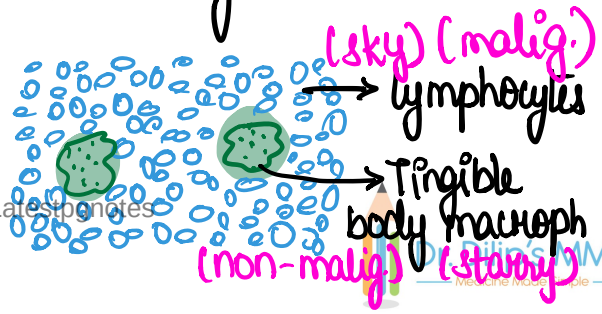
Burkitt's Lymphoma

Sporadic	HIV associated	Endemic
→ Abdomen	very rare	→ Jaw mass
→ ileocaecal mass (obstruction)		→ Maxillary/mandibular Bones
→ EBV (20%)		→ EBV (>90%)
→ Children/Adults		→ Children
		→ a/w P. falciparum? (±)

Cytogenetics – t(8;14) [75%] ⇒ ↑myc (myc amplification)

Markers –
CD 10 +
BCL6 + } ⇒ Germinal centre (GC) origin
Ki67 – ↑↑↑ (>90%) ⇒ Poor Prognosis
[Proliferation index]

Δ – ① LN Bx : Starry sky Pattern



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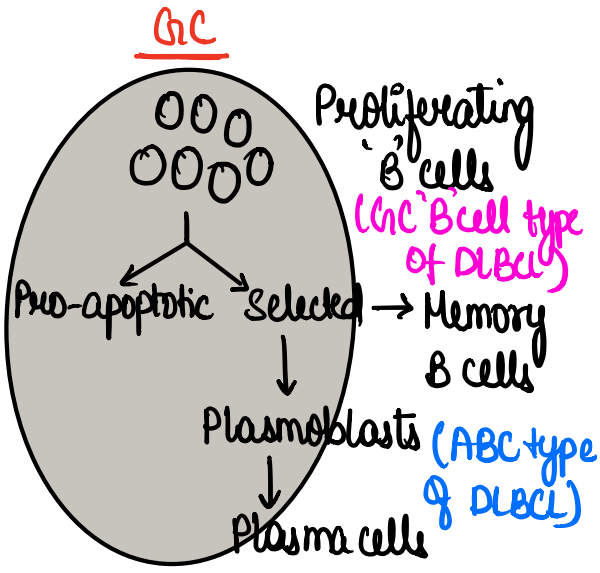
② DLBCL (Diffuse Large 'B' Cell Lymphoma):

→ m/c NHL in adults [overall m/c NHL]

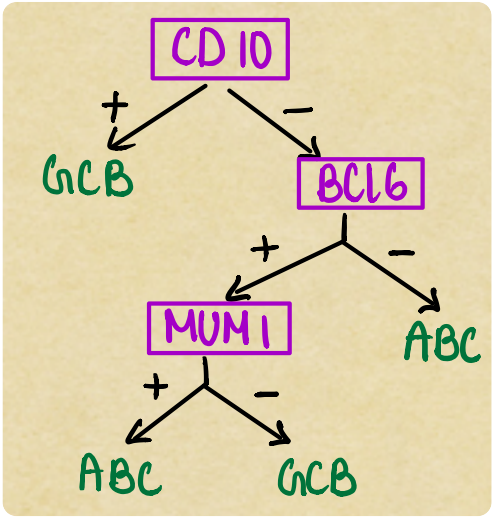
C/f – rapidly progressive painless Lymphadenopathy
+ B Symptoms ± Extranodal involvement (40%)

Markers – CD 19 +
CD 20 +
CD 22 +
CD 79 a +
PA X 5 +



Types – DLBCL

- **GCB type** (Germinal centre B cell type)
  - CD 10 +
  - BCL 6 +
  - MUM 1 –
  - t(14; 18)
  - good prog.
- **ABC type** (Anaplastic B cell type)
  - CD10 –
  - BCL2 +
  - MUM +
  - t(3; 14)
  - poor prog.



Morphological Classification: [given by WHO]

1. Centroblastic
2. Immunoblastic
3. Anaplastic
4. Plasmablastic

* 90% of 1° CNS lymphoma
↓
DLBCL

Scoring – International Prognostic Index

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③ Mantle Cell Lymphoma :

→ Common in older males (♂)

→ t(11;14) → ↑ Cyclin D_1

Markers – CD 5+ (Pregerminal)
CD 23– (rules out CLL)
CD 22+ (rules out CLL)

MCL	CLL
CD5+	CD5+
CD23–	CD23+
CD 22+	CD 22–

→ 'Angular nuclei' are seen

C/f – Intermediate [Rx / ↑↑ Relapse]

Extranodal – GIT ± BM infiltration
↓
Multiple Intestinal Polyps
Intussusception
Obstruction
} endoscopy & colonoscopy are done as routine procedures

Scoring : Mantle Cell Lymphoma International Prognostic Index

④ Primary Mediastinal Large 'B' cell Lymphoma :

→ DLBCL limited to mediastinum

→ anterior mediastinal mass ⟹ local invasion
± Superior Vena Caval Syndrome
± Effusions
± local C/F – Cough / SOB
Dyspnagia
Hoarseness
} → a/w ↑ fibrosis of mediastinum
↓
so, FNAC gives no result
↓
so, Mediastinal Surgical LN Biopsy is done (c̄ Chamberline anterior mediastinal scopy.

→ 1° mediastinal lymphoma (weak CD30+) (RS like synd.)
↓
is similar to HL (strong CD 30+) ≥ 80% cells
≤ 30% cells]

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→ no peripheral lymphadenopathy

* Double Hit/ Triple Hit Lymphomas } → myc ↑↑↑ + Bcl2/Bcl6 ↑ } → ↑↑ aggressive (poor)

SEVERITY SCORES :

FLIPI

Mnemonic : 'no LASH'

1. > 4 Nodal areas
2. ↑↑ LDH
3. Age >60
4. Ann Arbor Stage III/IV
5. Hb < 12g%

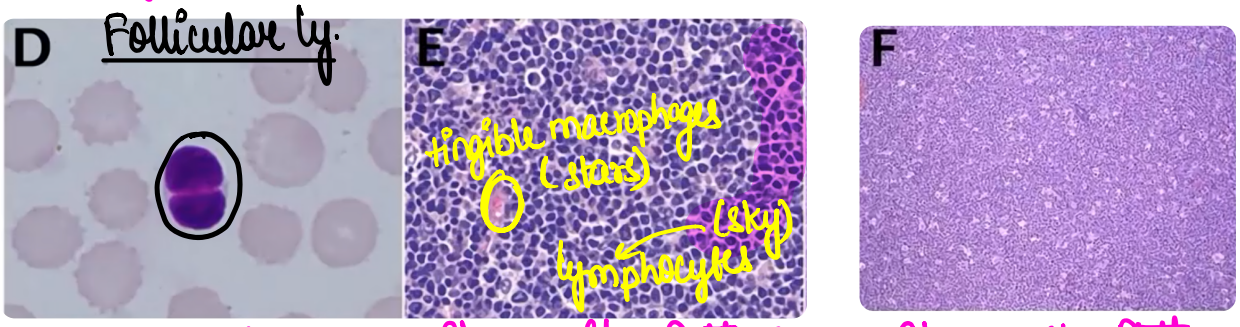
IPI

1. ≥ 2 Extranodal sites
2. ↑↑ LDH
3. Age >60
4. Stage III/IV
5. Performance status ≥ 2

MIPI

1. WBC count
2. LDH ↑
3. Age >60
4. ECOG status

Hairy Cell Leukemia — Fried egg cells — TRAP+ cells



Butt cells — Starry Sky Pattern — Starry sky Pattern (low power)

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T CELL LYMPHOMAS :

I. INDOLENT :

① Mycoses Fungoides :

T cell lymphoma
- SKIN, lymph nodes
- BLOOD (leukemic dissemination) → Sezary Syndrome + skin + lymph nodes

C/f : ① Skin – Erythematous/ Pruritic patches [Refractory to Rx]
± Erythroderma
± Alopecia

② LN – Common (local)
± Hepatosplenomegaly

Δ : ① Biopsy → ① Atypical lymphocytes
⇓
CD 4+ T cells [Cerebriform nuclei]
d/t clumping of chromatin

② Pautrier's microabscess
[epidermal infiltration of malignant cells]

II. AGGRESSIVE :

① Adult T cell Lymphoma :

→ Common in South East Asia/ Caribbean
→ exclusively seen in adults

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→ HTLV-I → 'TAX' protein → Adult T cell Lymphoma
(Oncoprotein)

Risk factors – ① Parenteral
② Breast feeding
③ Vertical transmission
④ IV Drug abusers

C/f – ① Acute (leukemic) → Hepatosplenomegaly ± Cutaneous lesions
(m/c)
± ↑ LDH
± ↑ Ca^{+2}
– Abd. pain
– Stones
– Psychiatric
– Bone lesions

② Chronic (lymphoma) → mild lymphadenopathy
± Stable lymphocytosis

Markers – CD4+
CD25+
CD7–
CD19/20–

② Aggressive NK Cell Leukemia :

→ EBV associated
→ 'B' symptoms + Multi Organ Dysfunction + Coagulation (DIC)

Types – ① Nasal
② Non-nasal

Markers – ① CD3/4/5/8 – (not 'T' cell)
② CD19/20 – (not 'B' cell)

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→ CD 16/56 + (NK cell)
CD 45 +
CD 68 − (r/o Histiocytic)

③ Large Granular Lymphocytes Leukemia :

→ ↑↑ LGL (BM/PS) → >500/μl [Ⓝ = 200-400/μl (10-15% of monoclonal cells)]

Splenomegaly, Cytopenias ↓ m/c − neutropenia → ↑↑ infections
↳ Fas mediated death

→ a/w ① RA (Felty's syndrome)
② Pure red cell aplasia
} ≥ 40%

LGL leukemias
- T-cell LGL → CD 3 +, CD 56 −
- NK cell LGL → CD 3 −, CD 56 +

④ Anaplastic Large Cell Lymphoma (ALCL):

Markers − CD 30 + (T cells)
ALK + (Anaplastic lymphoma kinase)

Cytogenetics − t(2;5)

→ a/w Silicone Breast Implants (♀)

→ Lymphadenopathy ± Hepatosplenomegaly

AIDS defining malignancy
① HPV ass. Cervical Ca.
② Kaposi Sarcoma (HHV 8)
③ Anal Ca.
④ NHL

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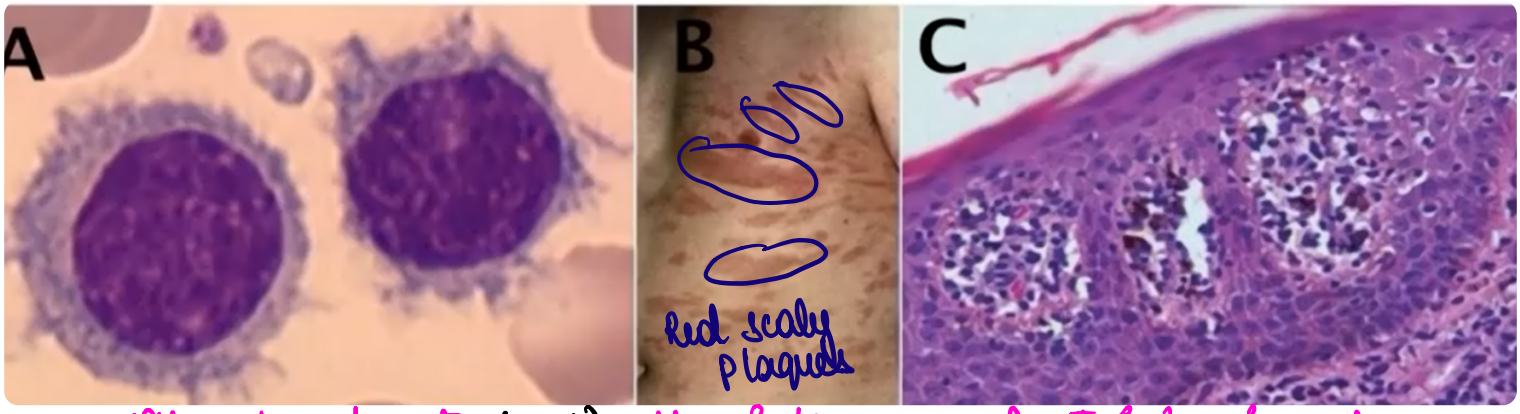
⑤ HIV associated NHL :

60-100 x association

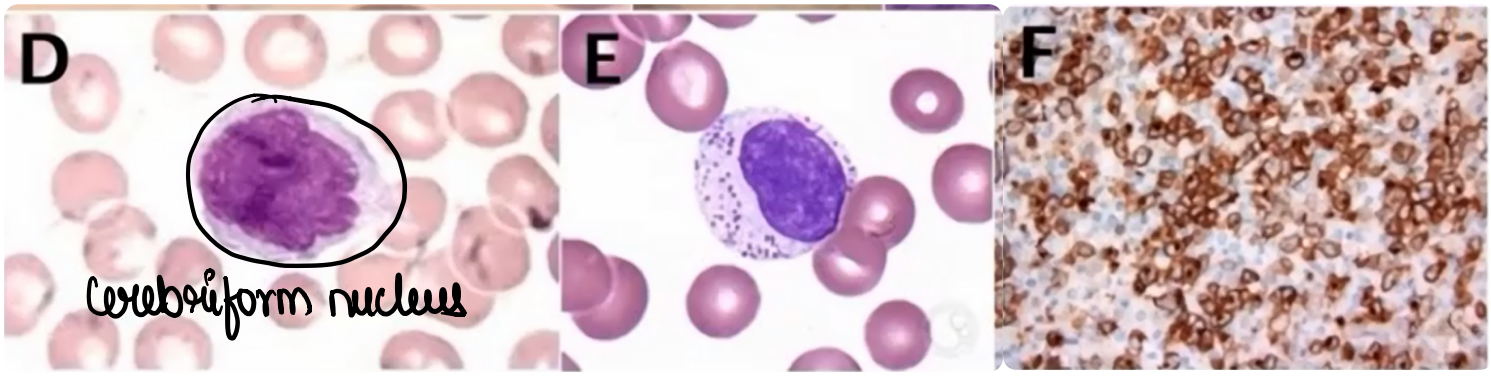
AID defining malignancy

① DLBCL (immunoblastic) (70%) ⇒ EBV + [CD4 < 100]
② Burkitt's lymphoma (20%) ⇒ EBV + [CD4 > 200]
③ 1° CNS lymphoma (15%) ⇒ EBV + [CD4 < 50]
④ 1° effusion lymphoma (<5%) ⇒ HHV 8

m/c 1° Brain tumor in HIV



Villous lymphocytes (MZL) | Mycosis/Sezary Synd. | Pautrier's microabscess



Sezary Syndrome (PS) | Lympho Granular Lymphocyte | ALK + ALCL

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Rx OF NHL :

Indolent

→ no cure
→ ↑↑ survival
Goal – ↓ symptoms

most imp. drug
Rituximab
(anti CD20)

Initial – ① RT (localised)
② Rituximab ± Chemo
↓
[Bendamustine
Cyclophosphomide
Fludarabine]

Alternate
↓
Obinutuzumab
+ Chemo

③ Ibrutinib

Maintenance – Rituximab

① Hairy cell leukemia – (BRAF V600E +)
– Fludarabine
– BRAF – → Vemurafenib
(Relapsed dis.)

② Gastric MALToma –
– H. pylori eradication
± RT

Aggressive

→ curable (probably)
→ ↓↓ survival (worse)
Goal – Cure
⇓
R-CHOP regimen

R – Rituximab
C – Cyclophosphamide
H – Hydroxydaunorubicine (Doxo)
O – Oncovin (Vincristine)
P – Prednisolone

① CNS prophylaxis :
– Intrathecal / Systemic Mtx
Indications –
① ≥2 LN site involvement
+ ↑ LDH
② Site (Danger) –
a) Paranasal sinuses
b) Testicular
c) Breast
d) Periorbital region
e) BM
f) Paravertebral

② Relapsed / Refractory :
① Salvage Chemo
② High dose chemo + Autologous HSCT
③ Allogenic HSCT (>2 relapses)

③ CART : [genetically modified TCRs] → CD19
eg: Axicabtagene ciloleucel / Tisagenlecleucel
↑ risk of CK release (cytokines)

④ Mantle Cell Lymphoma : Ibrutinib

⑤ Highly aggressive – Burkitt's lymphoma :
→ All pts must be given CNS prophylaxis + tumor lysis synd. prophylaxis
→ Rx – EPOCH-R
CODOX-M / IVAC
(High dose Cytarabine also included)

EPOCH-R
E – Etoposide
P – Prednisolone
O – Oncovin
C – Cyclophosphomide
H – Hydroxydaunorubicin
R – Rituximab

Rx – HL (vs) NHL :

HL
① Standard – ABVD ± RT
② Alternative – BEACOPP (Stage III / IV)
③ New – Brentuximab (classic HL)
Rituximab (NLP)

NHL – Rituximab

Low Risk	High Risk
Ritux + Chemo	R-CHOP
	MLL – Ibrutinib
	Burkitt's – EPOCH-R

New – Obinutuzumab
CARTs

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Chronic lymphocytic leukaemia

CLL/SLL :

→ m/c adult leukemia
→ most indolent NHL

Defect – Monoclonal Mature B cell Malignancy

Origin –

- Pre Germinal centre → unmutated IgVH → Poor Prog.
- not from Germinal centre
- Post-Germinal centre → Mutated IgVH → Good prog.
- (from memory B-cell)

→ **Malignant lymphocyte count** →

① CLL (Chronic Lymphocytic Leukemia) – >5000/μl
② SLL (Small lymphocytic lymphoma) – <5000/μl

→ Lymphadenopathy ± Hepatosplenomegaly } ⇒ seen in both CLL & SLL; but are more prominent in SLL.

Monoclonal B lymphocytosis :

→ ↑ lymphocytes (monoclonal)
→ + no CLL (because malignant lymphocyte count is < 5000/μl)
+ no SLL (because there is no Hepatosplenomegaly)
→ **Rx** : Observe!
→ Rate of Risk of transformation to CLL – 1%/yr

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C/f OF CLL/SLL:

→ CLL has no association with any CT/RT/Drugs, etc

① Asymptomatic – Incidental finding – Lymphocytosis only

② Symptomatic – ① B Symptoms → 10-20% cases
② Lymphadenopathy → 90% cases
③ Hepatosplenomegaly → 50% cases
④ AIHA / ITP
↓ 10% ↓ 1-2%
⑤ ↓Ig + Neutropenia → Recurrent Infections
⑥ BM failure → 15% cases
⑦ Monoclonal gammopathy → 5% cases

RICHTER Transformation:

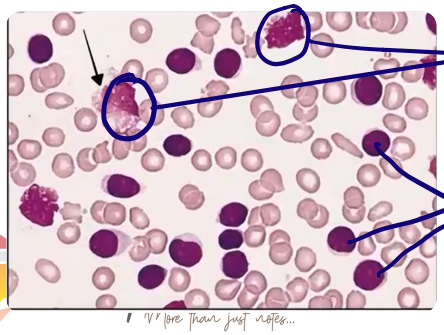
→ Transformation of CLL/SLL into aggressive mode (eg: DLBCL)

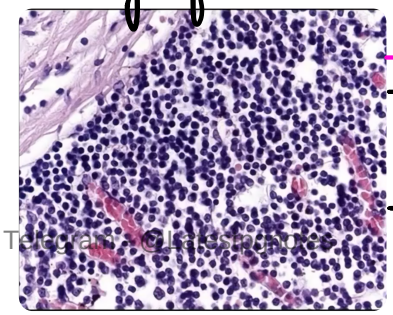
Features – ① New/worsening B symptoms
② Bulky Lymph nodes (previously small)
③ ↑↑ Sr. LDH

Risk – 5%

INVESTIGATIONS OF CLL/SLL:

① P.S – lymphocytosis (small)
– 'Smudge' cells → abⓝ B cells get smeared d/t shear stress during processing of slide





BM Biopsy
→ Infiltration of small lymphocytes (≥30%)
→ LN Bx also shows similar picture

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→ LN Biopsy shows 'Cleaved cells'

→ When Blasts ≥ 20% ⇒ Acute leukemia

② **Flow Cytometry:**

Surface Ig '+' → (dim)
CD 20 '+' → (dim)

CD 5 +
CD 10 −
CD 23 + (differentiates from Mantle cell lymphoma)

③ **Cytogenetics:**

Unfavourable ↓
① del. 11q
② del. 17p
③ Zap 70 +
④ CD 38 / CD39 +
⑤ Unmutated IgVH

Intermediate/ Neutral ↓
Trisomy 12

Favourable ↓
① del 13q (m/c)
② Zap 70 −
③ CD 38 −
④ Mutated IgVH

* del 13q has poor prognosis in Multiple Myeloma.

STAGING:

RAI staging

0 − Lymphocytosis only
1 − + Lymphadenopathy
2 − + Hepatosplenomegaly
3 − + Anemia (not AIHA)
4 − + Thrombocytopenia (not ITP)

BINET staging

A − < 3 node areas
B − > 3 node areas
C − Anemia / Thrombocytopenia (not d/t AIHA / ITP)

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Rx OF CLL/SLL :

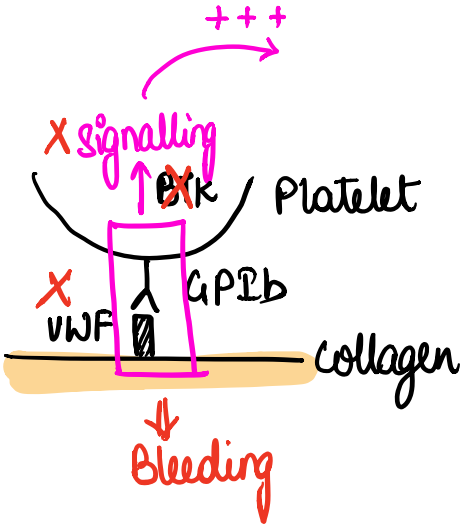
Indications :

① RAI score 3/4
② BINET score C } – Anemia / Thrombocytopenia
③ Disease related symptoms
④ Progressive diseases } 'B' symptoms, Recurrent Infections
⑤ AIHA / ITP + refractory to steroids

1st line Rx :

① Ibrotinib – [BTK⊖]

S/E – ① Atrial fibrillation
② HTN
③ Bleeding (d/t Platelet adhesion defect)
④ Pneumonia
⑤ ILD



→ [A 70 yr old pt. c̄ CLL + Atrial fibrillation & CHA_2DS_2 Vasc Score ≥ 2]
⇓
'Warfarin' given

* [Avoid Ibrotinib]

Other Drugs :

Fludarabine
Cycloptos / Bendamustine } ± anti CD 20 → Rituximab / Ofatumumab / Obinutuzumab
± anti CD 52 → Alemtuzumab

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Rare Drugs:

① Venetoclax [BCL2⊖] (BH3 Analog)
② Acalabrutinib [BTK⊖]
③ Idelalisib [PI3K⊖] ⟹ S/E – Colitis
Pneumonitis
Hepatitis
④ Allogenic HSCT

Prognosis – 10yrs survival

→ I.V Ig infusions can be given for recurrent infusions

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Plasma cell Dyscrasias

PLASMA CELL DYSCRASIAS :

① Multiple Myeloma

Variants – ① Non-secretory myeloma
② Asymptomatic / Smouldering myeloma
③ Plasmacytoma
④ Plasma cell leukemia

② MGUS → Monoclonal Gammopathy of Unknown Significance

③ Waldenstorm's Macroglobulinemia

④ Ig H deposition disease

⑤ POEMS → only place where osteosclerotic lesions (myeloma) is seen.

MULTIPLE MYELOMA :

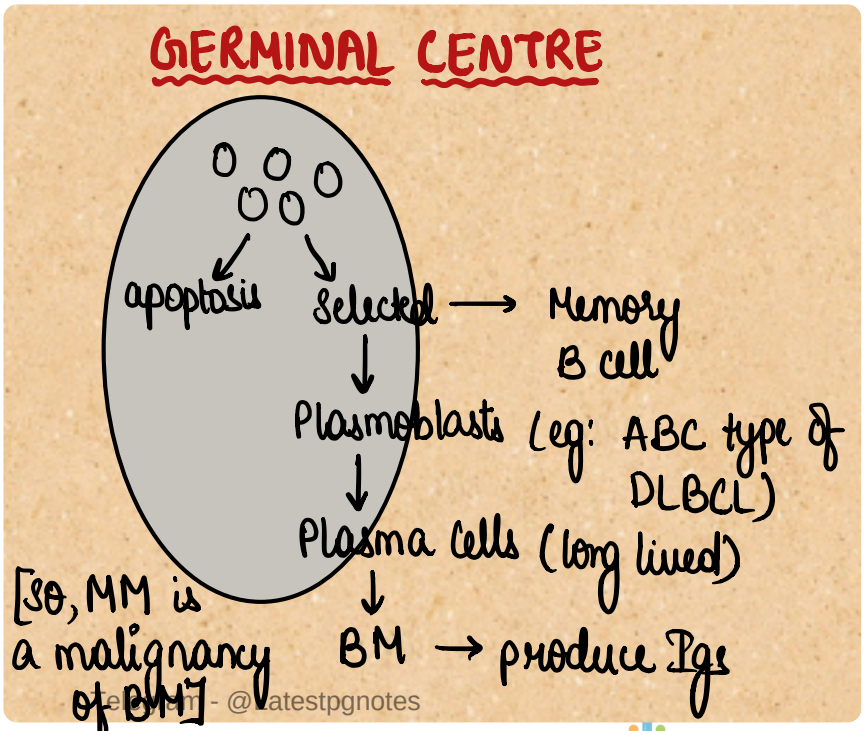
→ Monoclonal neoplasm of Plasma cells [Post Germinal Centre B-cells]

⇓

↑↑ Igs (dysfunctional)

↓ ⇓ ↑↑ Infections

① Amyloidosis (AL)
② Light Chain deposition Disease (LCCD)
③ Coagulopathy [AL binds to FX & ↓ it]
④ Neuropathy] ↓ d/t demyelination



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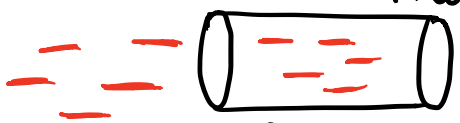
→ NF-kB is important for Plasma cells.

→ +++ Igs production
→ +++ Post G.C 'B' cells
→ ⊖ by Steroids

BORTEZOMIB ⊖ → Proteosome



IkB → taken into Proteosome ↓
⇓
↑↓ IkB
⇓
↓↑ NF kB ----> degraded

Lytic lesions in MM:

Plasma cells
↓
Macrophage inflammation Protein (MIP)

+++ → Stromal cells → RANK L (RANK ligand) —+++→ Osteoclasts → ↑ Bone lysis

⊖ → Osteoblasts → ↓ Bone formation

⇒ Pure lytic lesions [∄ any osteosclerosis]

Survival of Plasma Cells:

→ Plasma cells adhere to Stromal cells (for survival)
⇓
Growth factors released
⇓
Support Plasma cells

Clinical features:

① CRAB features → C → ↑ Calcium (40%)
– d/t +++ Osteoclastic activity

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→ +++ Osteoclastic activity

↑ Ca^{+2} ± ↑ PO_4^{2-}

↓ PTH (Parathyroid Hormone)

→ ⊖ Osteoblast activity

→ Alkaline Phosphatase – Ⓝ

R → Renal failure

- ↑ Sr. Creatine / Proteinuria
- Light chain deposition → T_2 RTA (Proximal)
  ↓
  AL Amyloidosis
- ↑ Ca^{+2} / ↑ uric acid / type I cryoglobulinemia

A → Anemia

- BM involvement (50-60%)
- Normocytic anemia

B → Bone lesions (m/c)

- lytic lesions
- Pathological #
- Bone pain (low back ache)

* Age of Presentation → ≃ 70 yrs
* Case: Elderly pt. (>60 yrs) → c/o Backache
  - features of AKI (Sr. Creatine ≃ 1.5-2.5)
  - ↑ urinary protein

→ Do screening for MM in these cases

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② Other features :

① Recurrent infections (immunoparesis)
↓
↑ ab ⓝ Ig ⟶ suppress ⓝ Ig production

② Neurologic symptoms → Neuropathy (↑ Ig)
Cord compression
POEMS

③ ↑ viscosity → d/t ↑ Ig
IgM > 4g/dl
IgG > 5g/dl
IgA > 7g/dl

④ Coagulopathy
⑤ Amyloidosis

Investigations :

① Paraprotein :

a) SPEP – Serum Protein Electrophoresis – 80%
b) SPI – Sr. Protein Immunofixation
} – 93%
c) UPEP – Urine Protein Electrophoresis
d) UPI – Urine Protein Immunofixation
} – 97%

① SPEP :

- depends on 'M spike' (but, this is produced by heavy chains)
- 20% – only light chains
- we have to further perform SFLC (Serum Free Light Chain) Assay
  UPI
  UPEP

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→ SPEP doesn't tell about the type of Paraprotein
→ Monoclonality cannot be confirmed.

② SPI – Paraprotein composition is shown
→ Monoclonality is confirmed
→ Ig A (50%) ; Ig A (20%) ; Ig D (2%) ; Ig M (0.5%)
Light chains only (20%)
→ Non-secretory myeloma → <5%
↓
– no Paraprotein produced
– all Paraprotein tests – '–ve'

③ UPEP, UPI } → useful for filtered light chains
→ 'Bence-Jones Proteins' are detected
→ they don't state the composition & monoclonality
→ SFLC assay has taken place of these UPEP & UPI

'M' spike:

Seen in →
- Monoclonal → MM, MGUS, CLL, Lymphoma, Sarcoidosis, RA, Sjogren's synd.
- Polyclonal → HIV, Rheumatic diseases, Cirrhosis

④ SFLC assay → Serum free light chain assay
– Most sensitive & most useful for Δ
– also useful for follow up
– only 20% → only light chains secreted.

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→ κ/λ chains (light chains)
⇓
Ⓝ = 0.6 (0.26 – 1.65)
→ either of the light chains is secreted (not both)

② Δ of lytic lesions :
→ By X-rays / MRI / PET-CT
→ Bone scans are not useful → because, osteoblasts do not take up Ca^{+2}

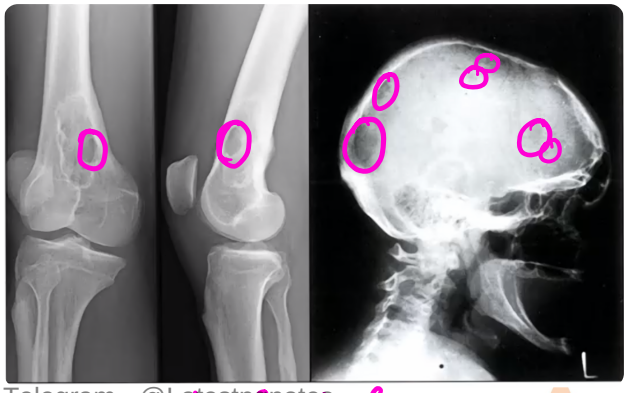
③ Tumor burden :
→ By LDH / β_2 microglobulin

④ Cytogenetics :

Standard risk	High risk
Hyperdiploidy	Hypodiploidy
t(11; 14)	del (17p)
Ⓝ Karyotype	del (13q)
	del (11q)
	t(4; 14)
	t(14; 16)
	t(14; 20)
	1q gain

→ Included in ISS (International Scoring System)

⑤ Immunohistochemistry :
→ By Flow cytometry
→ CD 20 –
CD 38 +
CD 138 +



Lytic lesions

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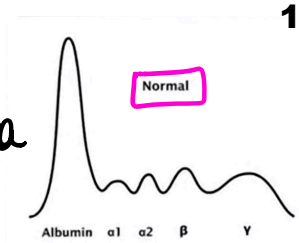
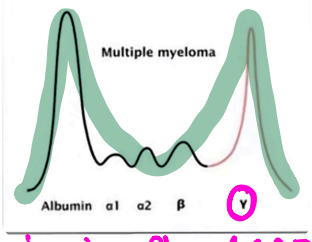
Criteria :

① BM Plasma cells ≥ 10% / Biopsy proven Plasmacytoma (Clonal)

+ ≥ 1 Myeloma Defining events





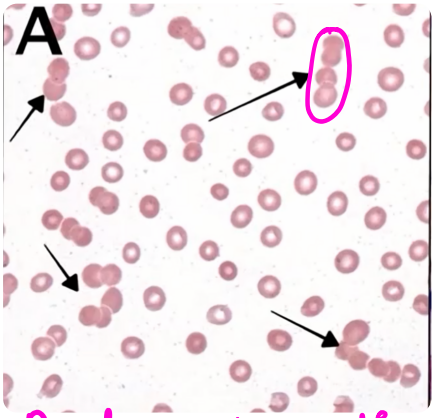
'M' spike (SPEP) (in γ globin)

Myeloma Defining events :

① RDTI = [CRAB] (Related Organ Tissue Involvement)

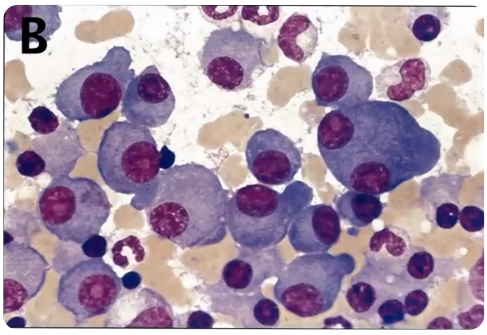
- Calcium > 11
- Creatine > 2 (Renal)
- Hb < 10 (Anemia)
- Lytic lesions (Bone)

② Other – a) BM Plasma cells ≥ 60%
b) SFLC ≥ 100 : 1
c) > 1 focal lesion on MRI



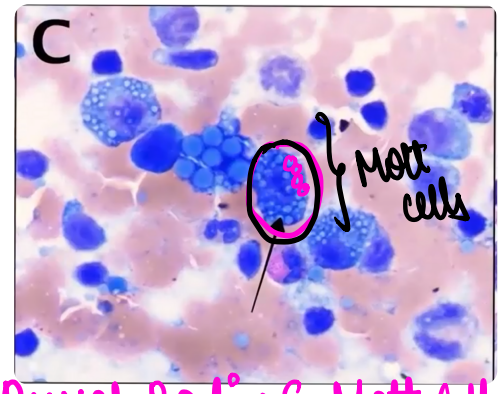
Rouleaux formation

Other findings → ↑↑ ESR
↑ Rouleaux formation

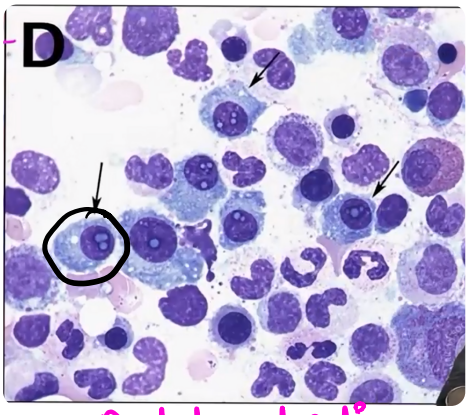


↑ Plasma cells

[Plasma cells have an eccentric cart wheel-like nucleus, cytoplasmic vacuoles composed of Ig]



Russel Bodies & Mott Cells



Dutcher bodies

Russel Bodies – Intracytoplasmic vesicular inclusion bodies.

Mott Cells → Plasma cells harbouring Russell bodies

Dutcher Bodies – Intranuclear inclusion bodies (Ig)

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	MGUS	Smouldering myeloma	MM	non-secretory myeloma	Plasmacytoid myeloma	WM
CRAB	No	No	Yes	Yes	No	No
Paraprotein	<3g/dl	≥3g/dl	≥3g/dl	<3g/dl	Variable	>3g/dl
SFLC	(N)/↑	↑↑	↑↑	(N)	(N)/↑	↑↑
Other Ig	(N)	↓↓	↓↓	(N)	Variable	↓↓
BM (Plasma cells)/LPL	<10%	≥10%	≥10%	≥10%	<10%	≥10% (LPL

* The only difference b/w a) MM & Smouldering Myeloma →
  MM- Symptomatic
  SM- Asymptomatic

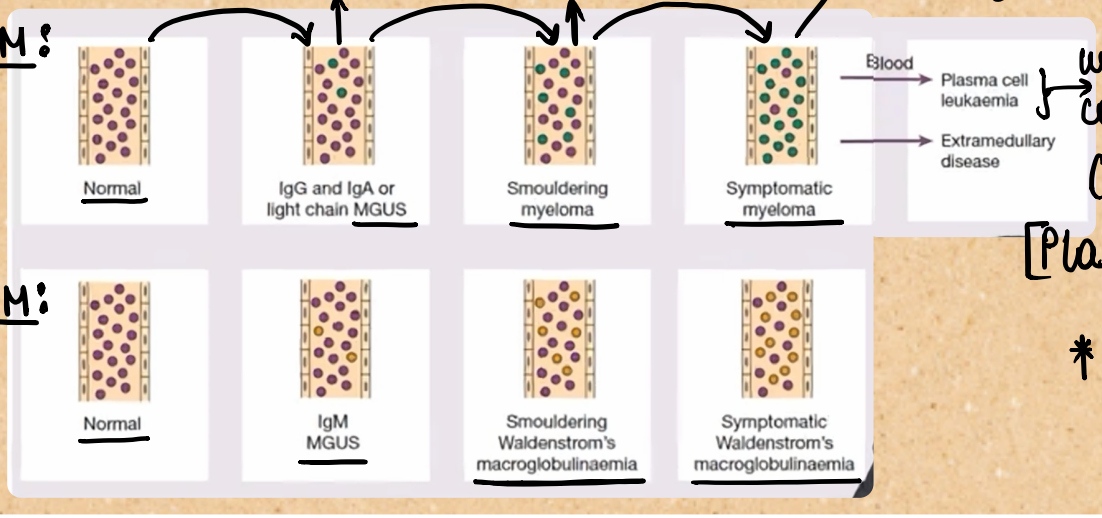
b) MM & Non-secretory Myeloma →
  MM- Ig/Paraprotein secreted
  NSM- " " no secreted

MM:

- Monoclonal Paraprotein <3g%
- No Symptoms

Paraprotein >3g%
NO CRAB

Paraprotein >3g%
CRAB +ve



when malig. Plasma cells come into blood (Plasma cell leukemia)
[Plasma cells >2000/μl]

WM:

* MM is preceded by MGUS

MGUS:

→ 25% of overall MM
→ transformation into MM → 1%/yr (risk)

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Transformation :

MGUS
- IgA/IgG type ⇓ MM
- IgM type ⇓ WM

SMOULDERING LYMPHOMA :

→ Asymptomatic [no CRAB]

→ Paraprotein >3g% ⟹ Rule out the presence of Occult lytic bone lesions by PET-CT/MRI. ⟹ Because their presence l/t Δ of MM

Rx - Observation (no Rx)

STAGING OF MM :

International Scoring System (ISS)

[Based on β_2 Microglobulin/albumin]

I - β_2M < 3.5 mg/dl + S.alb. > 3.5 g%

II - in between [eg: β_2M < 3.5 mg/dl, Alb < 3.5 g%]

III - β_2M > 3.5 mg/l

⇓

Revised ISS - includes LDH + Cytogenetics (most imp. - 17p del.)

Durie Salmon Staging

[Based on Hb/Ca^{+2}/lytic lesions/Paraprotein]

I - (All)	Hb > 10 Ca > 12 ≤1 lytic lesions	Paraprotein IgG < 5 IgA < 3	Urine Light chain < 4g/d
II -	In between		
III - (any 1)	Hb < 8.5 Ca > 12 > 5 lytic lesions	IgG > 7 IgA > 5	ULC > 12g/d

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Imp. Cytogenetics – del 17p
t(14;16)
t(4;14)

Survival – I stage – 60 months
II " – 40 months
III " – 30 months

Rx of MM:

① Proteosome ⊖ → Bortezomib → m/c used (gives as i.v.) → S/E – Peripheral neuropathy
2nd gen (Oral) – Carfilzomib, Ixazomib → less Peripheral neuropathy

② Immunomodulators → Lenalidomide, Thalidomide, Pomalidomide → ↑ Peripheral neuropathy
– Cytopenias
– thrombo-embolic manifestations

③ Others → ① Steroids (Dexamethasone)
② Melphalan
③ Panobinostat (HDAC ⊖) – [Histone Deacetase ⊖]
⇓
Heritable DNA changes / & DNA responsible for eg: skin, tongue, etc come under Epigenetics
(these DNA changes are not disease causing)

④ Elotuzumab [anti SLAM 7]
⑤ Daratumumab [anti CD38]
⑥ CART's [anti BCMA]
→ + NK cells

DNA suppression methods:

① DNA methylation [DNMT] ⇒
② Histone acetylation [HDAC] ⇒
} Silence the DNA repair genes
⇓
↑ Cancers
[eg: DNMT – hyperactivation causes MDS]

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④ Adjuncts – Bisphosphonates (to ↓ pathological #)
Radiotherapy
IV Ig (for recurrent infection)
Plasma exchange (for Acute Kidney Injury / Viscosity)

Rx

- Old (>77y) (or) transplant ineligible → Chemo → Induction ± Maintenance → Triple Rx (Proteosome ⊖, DEXA, Lenalidomide)
- Younger (<77yrs) + transplant eligible → Induction Chemo → High dose Melphalan → Autologous HSCT

① MGUS – Observation + SPEP (6 mon) $\xrightarrow{\text{Stable}}$ 1yr (annually)

② SM – close observation

③ Plasmacytoma – RT
- Osseous → Ribs / vertebra
- Extraosseous → Upper Respi tract > GIT

WALDENSTORM MACROGLOBULINEMIA :

→ B-cell neoplasm – Lympho Plasmacytoid lymphocytes

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Patho – 90% MyD88 [L265P ⟹ NFkB] [not seen in MM]

Pattern Recognition Receptors:

→ TLR ↘ ↙ CLR

MyD88 (Adapter Protein) → NFkB ⊕ ⟹ ↑ Pro inflammation

↑ RIG

→ NLRP → ⊕ Caspase

Pro IL-1β → IL-1β

C/f:

① No evidence of bone lesions [If there are bone lesions & IgM 'M' spike] ↓ MM / IgM Myeloma]

② IgM ⟹ 'M' spike

③ Fatigue

④ Anemia / Cytopenia
⑤ Hepatosplenomegaly
⑥ Lymphadenopathy
} (d/t) Tumor infiltration

⑦ Hyperviscosity (15%) ⟹ { Neurologic symptoms
Cardiopulmonary symptoms (SOB] ↓ either d/t CHF / Pulm. infiltrates)

D/t ↑ IgM → ① Hyperviscosity

② Type I Cryoglobulinemia

③ Platelet dysfunction → Bleeding

④ Deposition ⟹ Amyloidosis [Skin / Kidney / Intestine]

⑤ Chronic AIHA

⑥ Peripheral neuropathy

Abⓝ Abs ⇓ Auto Abs against [Myelin associated glycoprotein]

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MM → 'M' spike (>3g%) ← WM

MM	WM
→ Plasma cells	→ Lymphoplasmacytoid lymphocytes
→ MyD88 ✗	→ 90% ⊕ MyD88
→ IgG > IgA	→ IgM
→ CRAB features	→ No Bone lesions
→ Lymphadenopathy, Hepatosplenomegaly } rare	→ LAN, HSM } Common (++++)
→ ≥10% Plasma cells	→ ≥10% LPL
→ CD 20 −	→ CD 20 +
→ Hyperviscosity (rare)	→ Common

Investigations:

① SPEP / SPI → >3g% Paraprotein
M spike ✓ (IgM type)
Monoclonal

② BM Biopsy → ↑ LPL (≥10%)
CD 20+
CD 38+
CD 138+

③ β_2M → ↑↑ (Prognostic Marker)

Relative Serum Viscosity → $\frac{\text{Serum viscosity}}{\text{Viscosity of } H_2O}$ ⇒ (N) = 1.8

Hyperviscosity > 5-6

Rx: ① Hyperviscosity – Plasma exchange
② Symptomatic – Rituximab ± Chemo (Bendamustine, Cyclophosphamide)

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→ Ibrutinib + Rituximab
↓
blocks MyD88 pathway

Ig H DISEASE :

→ Clonal 'B' cell proliferation disorder
⇓
only Heavy chains

	C/f	Pathology	Comments
① α HCD (α Heavy Chain Disease) [a/w Campylobacter jejuni]	m/c → GIT (m/c) ↓ malabsorption Abd. pain Wt. loss	→ Jejunal mucosal infiltration [Plasmacytoid cells]	Extranodal Marginal zone lymphoma [MALTOMA] ↓ - α-HCD - Immunoproliferative Small Int. Disease (IPSID) [Seligman disease/ Mediterranean lymphoma]
② γ HCD	→ Systemic Symptoms → Lymphadenopathy → Hepatosplenomegaly → Anemia ± Palatal/uvular swelling	Polymorphic infiltrate	→ Franklin Disease [a/w lymphoma]
③ μ HCD	→ similar to CLL/SLL	- BM - vacuolated Plasma cells/lymphocytes [↓ Ig] Paraimmunoglobulinemia	→ Idiopathic

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Δ: ① SPEP → 'M' spike
② SPI → Composition (only Heavy chains)
(more imp. than SPEP)

Rx:

① α HCD – Antibiotics (initial)
Chemo Rx (late)

② γ HCD
③ μ HCD } – Chemo Rx

POEMS SYNDROME:

P – Polyneuropathy (100%)
O – Organomegaly
E – Endocrinopathy
M – Monoclonal proteins (100%)
S – Skin changes

} + Osteosclerosis
(so, also called Osteosclerotic syndrome)

Criteria:

Mandatory	Major	Minor
① Polyneuropathy	① Sclerotic bone changes	① Organomegaly
② Monoclonal ↑ Ig	② Castleman disease	② 3rd space collection/oedema
2/2	③ ↑↑ VEGF	③ Endocrinopathy
	1/3	④ Skin changes
		⑤ Papilloedema
		⑥ Thrombocytosis/ Polycythemia
		1/6

Δ – 2 + 1 + 1

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Basics of Acute Leukaemia

'Acute' 'Leukemia': ↑ of Blasts in BM (Acute)
↑ WBC in BM & Blood (Leukemia)

PATHOGENESIS:

(Clonal Proliferation)

Hematopoietic Progenitor cells
↓ fails ⇒ Blasts in BM ⇢ ↓ (N) Lineages
Differentiate
Blasts in BM ⇢ Spill ⇢ Peripheral Blood
↓ (N) Lineages ⇢ Cytopenia ⇢ Peripheral Blood

	AML (m/c)	ALL
① Epidemiology	– 7th decade (68 yrs)	– Bimodal → 1st decade (3-7yrs) → Elderly [Almost 80% of ALL within 6 yrs of age]
② C/f:	– occurs when Blasts > 50,000 ① Leukostasis [SOB/CXR infiltrates/Blurring of vision/TIA/Stroke ② DIC ⇢ AML-M3 [Acute Promyelocytic Leukemia] ③ Chloroma ④ Lymphadenopathy/HSM (M4/M5) – relatively common	① Bony/lumbar pain ② Lymphadenopathy/Hepatosplenomegaly ③ SVC syndrome ④ CNS involvement (10%) ⑤ Tumor lysis syndrome

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Chloroma :

→ Extramedullary collection of Blasts

→ Also known as Granular Sarcoma / Myeloblastoma

Site – ① Skin (m/c) – (Extremities) ⇒ 'LEUKEMIA CUTIS'
② Gingiva
③ Peri-orbital

→ Seen in – a) AML – M_4 } CD 13 +
b) AML – M_5 } CD 14 +
c) AML – M_2 → t (8; 21)

M_4 – inv (16)

→ Biopsy – modified Monocytes [Arbiskov Cells]

Common features of AML & ALL :

① Cytopenias → a) Anemia → fatigue
b) Neutropenia → recurrent infection
c) Thrombocytopenia → bleeding

INVESTIGATIONS :

① Peripheral Smear – Cytopenias
[Blasts >95%] ± Auer rods [AML]

② Flow Cytometry / IHC – CD markers

Myeloid	Lymphoid
Precursors – CD34 / CD45 / Tdt +	B Lymphoid – CD19 +
Myeloid – CD 13/33 / CD117 / CD15	CD 20 +
CMPO (Cytoplasmic MyeloPeroxidase)	CD 10 +
	CD 22
	CCD79a

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Monocyte – CD 11b/11c / CD14 / CD 64 / CD15
– lysozyme

Erythroid – CD71 / CD235a [Glycophorin A]

Megakaryocyte – CD 41 / CD 61

T Lymphoid – CD3 → Pan T cell marker, CD7, CD5, CD2, CD1a, CD4/8

NK cell – CD 16/56

③ Cytochemistry :

	AML	ALL
① MPO	+	–
② Sudan Black	+	–
③ PAS	+ (AML M6) [Fine Blocks]	+ [Coarse, Granular]
④ NSE	+ (AML M4/M5)	–
⑤ Acid Phosphatase	+ (AML M6) [diffuse staining]	+ (T-ALL) [golgi staining]

④ Bone Marrow Aspiration :

$\geq$ 20% blasts + Hypercellular —sent for→ a) HPE, b) Cytogenetics, c) Flow Cytometry

20% → not always ⇒ Cytogenetics

- t (15; 17)
- t (8; 21)
- inv (16)
- t (16; 16)

} Δ regardless the blast %

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⑤ Lumbar Puncture :

→ to give Intrathecal ℞ in ALL

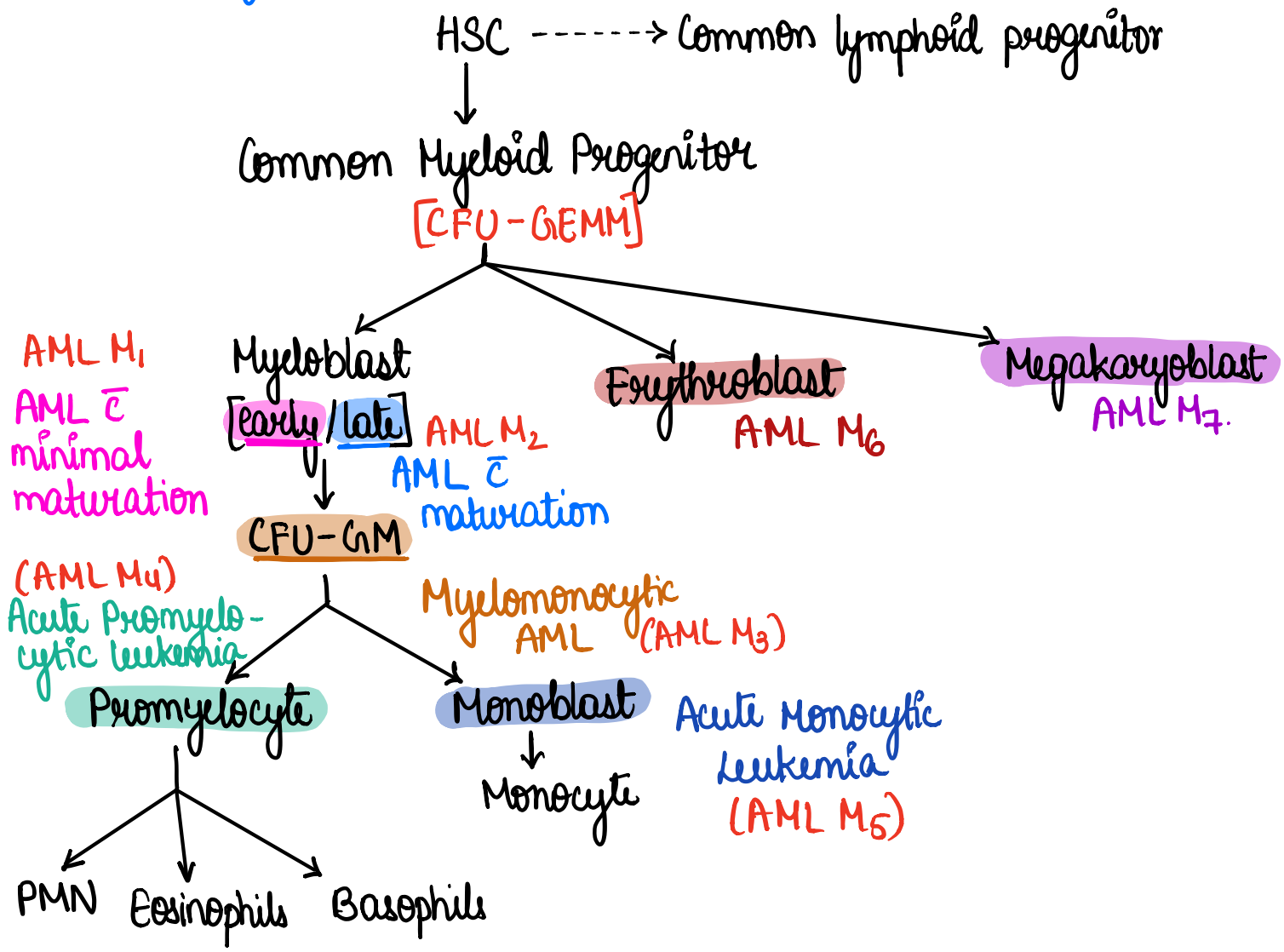
→ prophylactically also if CNS is involved in any leukemia

Acute Myeloid Leukaemia

ACUTE MYELOID LEUKEMIA:

→ AML – ↑ Blasts in blood & BM.

FAB classification:



	MPO	SBB	PAS	NSE	AUER RODS	CD MARKERS
M0	–	–	–	–	–	CD 13/33 +
M1	+	+	–	–	+	
M2	++	++	–	–	++	
M3	++++	++++	–	–	++++	

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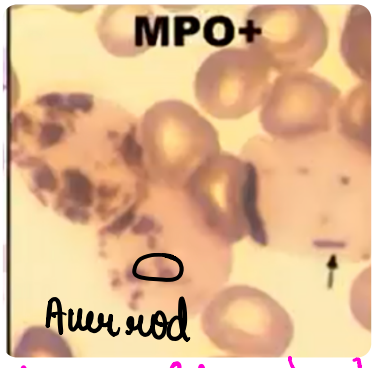
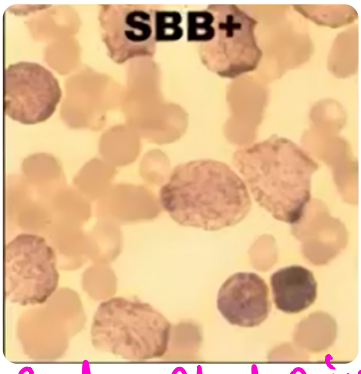
	MPO	SBB	PAS	NSE	AUER RODS	CD MARKERS
M_4	++	++	−	+	++	
M_5	−	−	−	+++	−	
M_6	−	−	+++ (Fine Blocks)	−	−	
M_7	−	−	Variable	−	−	

MPO – Myeloperoxidase
SBB – Sudan Black B
Auer rods

} Markers for Blasts of Myeloid Origin

① 



Myeloperoxidase '+ve' Sudan Black B '+ve' NSE '+ve' PAS '+ve'
(Markers for Myeloid lineage)

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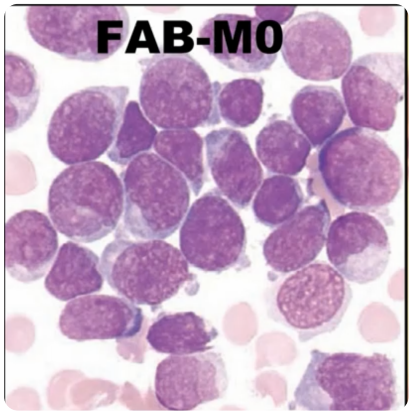
② M_0 

→ **AML ∅ Maturation:**
→ large agranular blasts
→ Auer rods '−ve'
→ MPO − / PAS − / SBB − / NSE −
→ CD 13/33 +
CD 117 +
CD 34 ±
HLA DR4 ±
→ No associated cytogenetics

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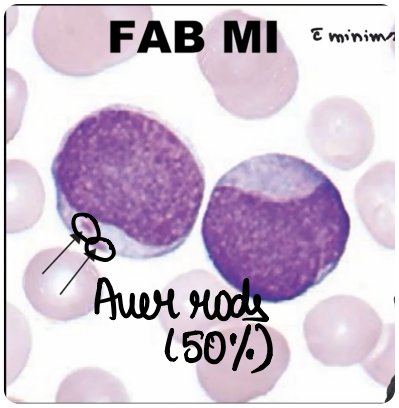
③ M_1



→ **AML c̄ Minimal Maturation:** (< 10% maturation beyond myeloblast)

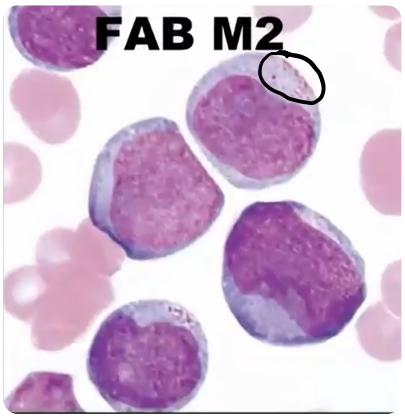
→ MPO + / SBB + / NSE − / PAS −

→ **Cytogenetics:** Trisomy 8
Ph + [t(9;22)]

[MPO > 3% staining is +ve
MPO < 3% staining is −ve]

---

③ M_2



* m/c type of AML

→ **AML c̄ Maturation:** [> 10% maturation beyond myeloblast]

→ MPO + / SBB +
NSE − / PAS −

→ Auer rods − 70%

Cytogenetics → t(8;21) → RUNX1 − RUNX1T1
t(6;9)

→ ↑ risk of Chloromas / leukemia cutis [d/t t(8;21)]

→ CD 13/33 +

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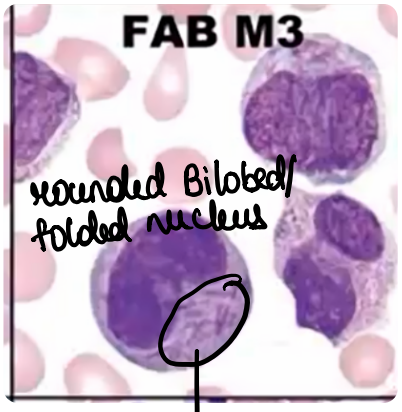
④ M_3



→ hypergranular

→ +++ Auer rods

→ Cell c̄ ↑↑ Auer rods
↳ Faggot cell

Markers: CD 13/33 +
HLA DR −
CD 34 −

→ **Acute Promyelocytic Leukemia:**

→ MPO +++ / SBB +++ / Auer rods +++
NSE − / PAS −

→ **Cytogenetics** − t(11;17) − common in children
− t(15;17) − common in adults
(15 → PML, 17 → RARA (Retinoic acid Receptor α))

→ **Importance of RARA:**

↑↑ Promyelocyte

t(15;17)
⇓
RARA disruption

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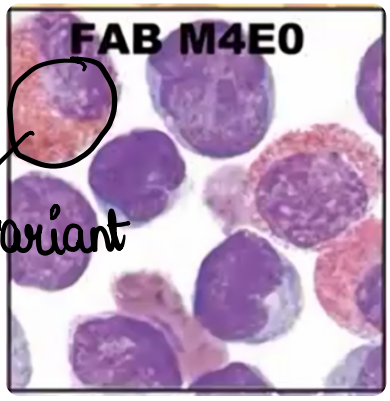
⑤



EO variant

M4

→ **Acute MyeloMonocytic Leukemia:**

→ >20% granular differentiation ⇒ MPO+ / SBB+
>20% monocytic differentiation ⇒ NSE +

→ Auer rods +

→ ↑ risk of chloromas / leukemia cutis

Markers – CD 13/ 33 +
CD 11b/ 14 + (states monocytic differentiation)

Cytogenetics – ① inv (16) ② del 16q ③ t (16;16)

Variant – M4 + Marrow Eosinophilia
[M4 EO Variant]

→ ↑ Lysozyme / ↑ muraminidase

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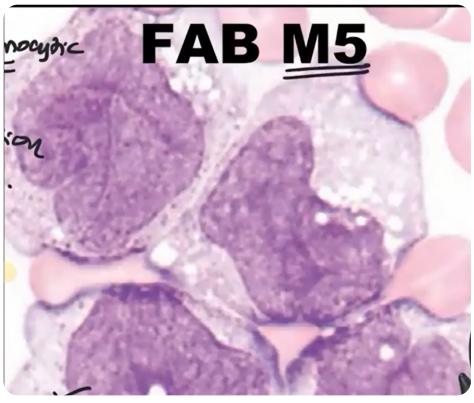
⑥



M5

→ **Acute Monocytic Leukemia:**

→ >80% Monocytic differentiation ⇒ NSE +++
<20% Granulocytic differentiation ⇒ SBB⁻ MPO⁻

→ Auer rods '-ve'

Markers – CD 11b / 14 +
CD 13/ 33 +

→ ↑↑ lysozyme / ↑↑ Muraminidase

Cytogenetics – del 11q
t (9;11) → MLLT3 : MIL
t (11;19)

Variants – ① >80% Monoblasts → Monoblastic leukemia
② >80% Promonocytes → Monocytic leukemia

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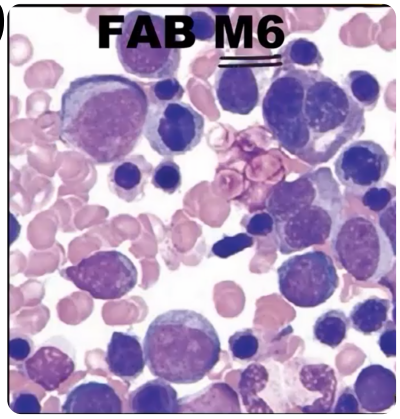
⑦



M6

→ **Acute Erythroblastic Leukemia:**

Cell of origin – Proerythroblasts

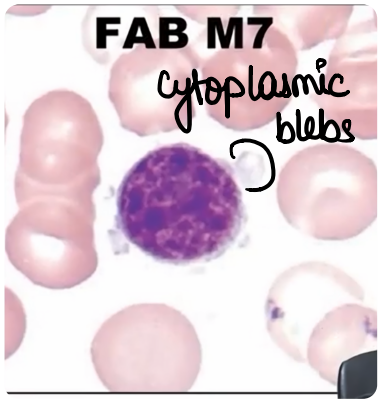
Malignant cell – Multinucleated, Vacuolated,
– Megaloblastoid change
– Cytoplasmic budding

Ab(n) lineages –

Erythroid Precursors (≥ 50%)	Non-erythroid cells (≥ 20%)	Pure Erythroid (100%)
↓	↓	↓
→ PAS +++ (fine blocks)	→ MPO +	→ PAS +++
→ CD 71/235a	SBB +	CD 235a/CD71 +++
↓ T.R, ↓ G.P.A	→ CD 13/33 +	→ MPO –
		SBB –
		CD13/33 –

---

⑧



M7

→ **Acute Megakaryocytic Leukemia**

→ Malignant megakaryocytes have Cytoplasmic projections / blebs.

→ ↑ PDGF ⇒ BM fibrosis ⇒ Dry tap on BM Aspiration
⇓
take BM Biopsy

→ MPO –
SBB –
NSE ±
} Variable

PAS ± (variable)

→ Platelet Peroxidase +

Markers –
→ CD41/61 +
→ GPIIb/IIIa +
→ vWF +

Cytogenetics – t(1;22) → infants
del 3q → adults

* Down's syndrome has ↑ risk of M7

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	Staining	CD markers	Comments
M_0	–	13/33 +	–
M_1	SBB/MPO +	13/33 +	may be Ph.+
M_2 (m/c)	SBB/MPO + Auer rods +	13/33+	t (8; 21) ↑ chloromas
M_3	SBB/MPO ++++ Auer rods +	13/33+	t (15 ; 17)
M_4	++ SBB MPO NSE	13/33 + 11b/14 +	inv (16) [Chloroma/ Leukemia cutis] t (16; 16) Eosinophils
M_5	++ (NSE only)	13/33 + 11b/14+	t (9; 11) (↑ risk of Chloroma/Leukemia cutis)
M_6	+++ (PAS)	71/235 a+	–
M_7	Variable	41/61+	t (1; 22) Cytoplasmic blebs BM fibrosis Down syndrome

WHO CLASSIFICATION :

① AML c̄ recurrent genetic abnormalities

② AML c̄ MDS related } Poor Prognosis

③ Treatment related AML

④ AML Not otherwise Specified (NOS)

⑤ Myeloid Sarcoma (a/w Sarcomas & extramedullary manifestations)

⑥ Myeloid leukemia a/w Down's syndrome (Poor prognosis)

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CYTOGENETIC ABNORMALITIES:

Favourable

1. APL [t(15;17)]
2. t(8;21)
3. inv (16)
4. Mutated NPM1 $\bar{c}$ FLT3-ITD
5. Biallelic mutation in CEBPA

Intermediate

1. Mutated NPM $\bar{c}$ FLT3-ITD
2. t(9;11) MLL-MLLT3
3. In between [favourable & Adverse]

Adverse

1. del 5q
2. del 7
3. t(6;9)
4. * t(9;22) – Ph+ (most imp.)
5. inv (3)
6. wild type NPM1 & FLT-ITD (High)
7. TP53/ASXL1

FLT3 mutations:

- ITD (Internal Tandem Repeats) (m/c)
- TKD (Tyrosine Kinase Domain)

Rx:

1. AML except APL:

1. Induction – 7 + 3 Protocol
   - [D1-7] → Ara-C (Cytosine Arabinoside)
   - [D8-10] → Anthracycline (Bolus) → Liposomal doxorubicin (or) Daunorubicin
     - age < 60: high dose (90 mg/m²)
     - age > 60: Std. dose (60 mg/m²)

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Newer Protocol → Depending on Age & fitness

- **Fit (Age < 75)** ↓
  - a) FLT3 – ITD/TKD mut.
    → 7+3 Protocol + Midostaurin
  - b) Core Binding factor +ve [t(8;21) (or) inv(16)]
    → 7+3 Protocol + Gemtuzumab (anti CD 33)
  - c) 2° AML (MDS/treatment related) [CDX 351]
    → Liposomal Ara-C + Liposomal doxorubicin
- **Unfit (Age > 75)**
  Venetoclax + 1/2 of Azacitidine
  (BCL2 –)
  Low dose Ara-C

② **Consolidation**: [after complete remission]

- Favourable risk ⇓ Hi DAC (High dose Ara-C)
- High risk ⇓ Allogenic HSCT

COMPLETE REMISSION

- **Morphologic**
  1. ANC > 1000
  2. Plt > 1,00,000
  3. No Extra-medullary dis.
  + 5% Blasts
  + no Auer rods
- **Cytogenetic**
  1. (N) cytogenetics ⇓ measured by FISH
- **Molecular**
  1. '–ve' molecular markers ⇓ by Flow cytometry

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③ Refractory/ Relapsed :

① FLT3 – ITD / TKD mutation → Crilotinib
Quizartinib

FLT3 ⊖ :

Type 1 ⊖ (ITD + TKD) ↓
- Sunitinib
- Midostaurin
- Lestaurtinib
- Crilotinib (2nd gen)
- Crenolanib (2nd gen)

Type 2 ⊖ (ITD only) ↓
① Sorafenib
② Ponatinib
③ Quizatinib (2nd gen)

approved for relapse

② IDH1 mutation :
a) Ivosidenib
b) Enasidenib

③ IDH2 mutation
a) Enasidenib

② Rx of APL : [APL → WBC Ⓝ / slightly ↑]

① ATRA (All trans Retinoic Acid) [Gold Std.]
② ATO (Arsenic Trioxide)

S/E of ATRA :

① Differentiation Syndrome
– ↑ granulocytes (WBC ↑↑↑)
↓
↑ Cytokines

t (15; 17)
↓
PML – RARA
↓↑↑ Promyelocyte
ATRA → ⊥ RARA
PMN ✓ Eosino ✓ Baso ✓

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⇓
↑ Capillary leak
↓
a) fever
b) SOB (CXR infiltrates)
c) Edema
d) Hypotension
e) AKI

Case – H/o APL
+ H/o ATRA use

⇒ Rx – DEXA (Steroids)
+ Supportive care
* Stop ATRA temporarily

Rx of APL:

- Non-high risk
  - ↓
  - WBC < 10,000
  - + t(15;17)
  - ↓
  - ATRA + ATO
  - [Induction + 4 cycles of consolidation]
- High risk
  - ↓
  - WBC > 10,000
  - ↓
  - ATRA + ATO + Chemo (Doxorubicin/ Gemtuzumab)

Summary of Rx of AML:

- AML except APL
  - ↓
  - Chemo
    - Induction
      - ↓
      - 7 + 3
        - Ara-C
        - Dono
      - ± Midostaurin
      - ± Gemtuzumab
    - Consolidation
      - ↓
      - HiDAC (04)
      - Allogenic HSCT
    - failure of CR
      - ↓
      - – α'gen
      - FLT 3⊖
      - – IDH⊖
    - relapse
- APL
  - ↓
  - ATRA + ATO
  - ↓
  - S/E – Differentiation Syndrome

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PROGNOSIS :

→ Age
H/O MDS / Rx / MPN
Cytogenetics
} considered for Prognosis

	GOOD	INTERMEDIATE	POOR
Cytogenetics	t (15;17) t (8;21) Inv (16)	Ⓝ	- del 5 / del 7 - TP53 - Complex Karyotype [>3 unrelated abⓝ Karyotype]
Molecular	- NPM ₵ FLT3 - CEBPA	NPM ₵ FLT3	Wild type NPM (↑↑ FLT3)
BM response to Rx	Complete Remission (<5% Blasts after 1st course)		>20% Blasts
Age	Child	Adults <60yrs	>60 yrs
Performance status	Good		Bad
Comorbid status	-		+
WBC	<10,000		>1,00,000
2° AML	No		Yes
MRD in remission	No		Yes (>0.1% of malignant cells)

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Acute Lymphoblastic Leukaemia

	Acute Lymphoblastic Leukemia	Acute lymphoblastic lymphoma
	Leukemic	Lymphoma
Blasts is BM	≥ 20%	< 20%
Lymphadenopathy	±	+++ (mass lesion)

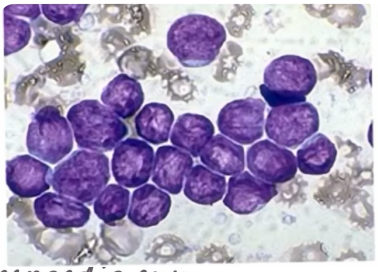
LAB FEATURES OF ALL :

① Cytochemistry → Tdt ⊕ (>95% cases)
↓
Terminal deoxyribosyl transferase
→ No granules

② Immunohistochemistry → Precursors (CD 34 / Tdt +)

B cell	T cell
(Pan 'B' cell) CD 19	CD 3 + (Pan 'T' cell)
CALLA → Common ALL Antigen	CD 10
CD 20	CD 2 +
CD 22	CD 5 +
CD 79a	CD 7 +
	CD 3 + (cytoplasm)

CLASSIFICATION :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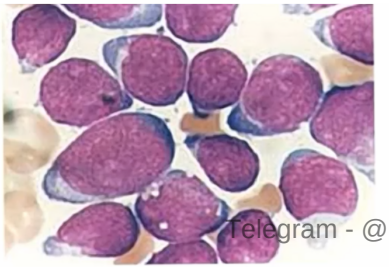
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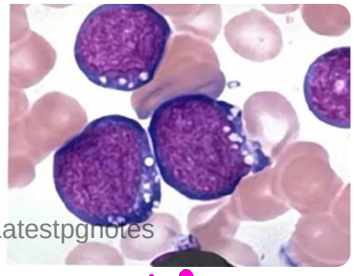
L3

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L1	L2	L3
① Small, Homogenous cells	① Large, Heterogenous Cells	① Large, Homogenous cells
② Scanty cytoplasm	② Moderate to Abundant	② Moderate to abundant
③ less Basophilic cytoplasm	③ less Basophilic	③ Intensely Basophilic + Prominent vacuolisation
④ Nucleus - Small/regular & Homogenous nucleus [no nucleoli]	④ Variable size/heterogenous nucleus c̄ irregular clefts + nucleoli	④ Stippled regular homogenous nuclei c̄ prominent nucleoli

WHO CLASSIFICATION OF ALL :

Philadelphia chr. [incidence ∝ age]

Based on Cytogenetics

(m/c) Pre-B ALL (85%)

worst prog *
① t (9; 22) – Philadelphia chr.

Infants
② t (11; 23) – MLL rearrangement

③ t (1; 19) – TLF 3 – PBX 1 (elongation factor)

Children
④ t (12; 21) – ETV 6 – RUNX1

⑤ Hyperdiploid (>50)

⑥ Hypodiploid

⑦ t (5; 14) ⇒ IL3 – IgH (Heavy chain)

(Adults)

Pre-T ALL (15%)

↓

d/t activation of NOTCH signalling

⇓

WBC ↑↑
Mediastinal mass
Pleural effusion

They are present in B-cell ALL also. But, these are more in favour of T-ALL [T-ALL >>>> B-ALL]

Rx OF ALL :

① Induction Rx :

- **Philadelphia chromosome '+ve' (25%)**
  ↓
  Chemo Rx / Steroid
  + Tyrosine Kinase ⊖

- **Other Mutations**
  - **Age <40yrs**
    ↓
    VADD
    [Vincristine
    Asparginase
    Doxorubicin
    DEXA]
    (Asparginase ↓ Pegylated)
  - **Age >40yrs**
    ↓
    Hyper CVAD
    - Hyperfractionated Cyclophosphamide
    - Vincristine
    - Anthracycline
    - DEXA

② CNS Prophylaxis :

→ Intrathecal Mtx + Cytarabine
± Whole Brain Radiotherapy (WBRT)

③ Post-Remission Rx :

- **Std. Risk Pts**
  ↓
  Consolidation Rx
  (for 7 months)
  ⇓
  Maintenance Rx
  (2-3yrs)

- **High Risk Pts**
  ↓
  High dose Chemo
  + Allogenic HSCT
  (once achieved complete Remission)
  ↓
  < 5% Blasts in BM

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PROGNOSTIC FACTORS :

	Standard Risk (Good Prog.)	Poor Prog. (High/Poor Risk)
① WBC	Low B cell: < 30000 T cell: < 1,00,000	High B cell: > 30,000 T cell: > 1,00,000
② Age	Child (< 1 yr)	< 1 yr / Adult
③ Type	B-ALL (child) T-ALL (adults) CD 10 (CALLA) +	B-ALL (Adult) T-ALL (child)
④ Cytogenetics	Ⓝ Hyperdiploidy t(12;21) - ETV-RUNX1	- t(9;22) (Philadelphia+) ↓ (20-30% incidence) - t(11;23) (MLL) - Hypodiploidy (< 44) - t(1;19) (AML-Tel1) - JAK 2 mutations (Down's synd.) - Complex Karyotype (> 5 Phenotypes)
⑤ Time to clear blasts from blood	< 1 wk	> 1 wk
⑥ Remission time	< 4 wks	> 4 wks
⑦ CNS disease	–	++
⑧ Minimal Residual Disease	– [@ 1 mo → child @ 3 mo → adults]	++ (@ 3-6 mo)

↓

Minimal Residual Disease is measured by Fluorescence Activated Cell Sorter

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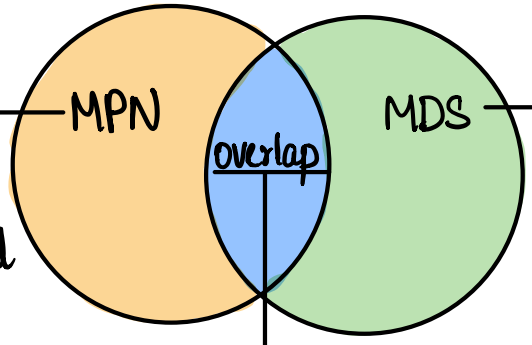
Myeloproliferative Neoplasms - I

PATHOGENESIS :

Myeloid Precursor cell (↑ Blasts)
↓ Failure — l/t Leukemia
↑ differentiate & mature ↓

MPN

defective ↓ dysplastic (MDS)



↑ cell proliferation
- BM ↓ ↑ Cellularity
- Peripheral ↓ ↑ cells
- no dysplasia

defective proliferation
- Periphery ↓ cells (cytopenias)
- BM ↑ cells
- dysplastic cells (morphologically abⓝ cells)

eg: JMML, CMML

MPN + MDS
- ↑ cells in Periphery & BM (Monocytes)
- Dysplastic [aCML — atypical CML, SETP1 mutation]

Diseases of MPN :

① CML → Philadelphia Chr. should be '+ve' [100% rule] — t(9;22)

② PV (Polycythemia Vera)
③ ET (Essential thrombocytosis)
④ PMF (1° Myelofibrosis)

→ JAK 2 (m/c) — V617F (m/c), Exon 12
CALR
C-MPL (rare) (codon 515)

⑤ Systemic Mastocytosis → C-Kit (D816V)

⑥ Myeloid neoplasms c̄ marrow eosinophilia → PDGFRA/PDGFRB

⑦ CNL (Chronic Neutrophilic Leukemia) → CSF3R

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→ Hyper Eosinophilic Syndrome → also has PDGFRA mutation

→ All the above mentioned disorders i.e. :

MPN
MDS
Overlap } ⇒ Acquired Clonal defects (Precursor Stem Cell mutation)

⇓

All these can transform into AML, if there is continuous clonal defect (because, cells completely fail to differentiate)

⇓

This AML transformation has poor prognosis

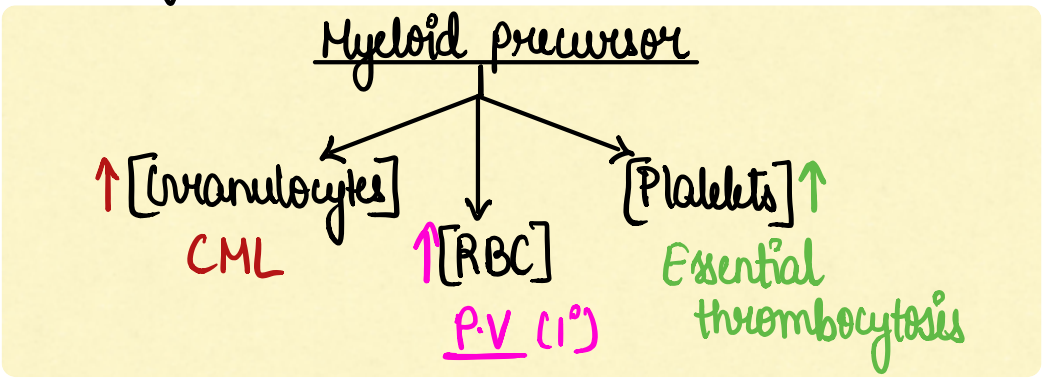
POLYCYTHEMIA VERA :

→ ↑ RBC masses ± granulocytes ↑ (50%) ± ↑ Platelets (50%)

⇓

∄ Physiological stimulus

→



→ ERYTHROCYTOSIS :

- Relative
- Absolute
  - 1°
  - 2°

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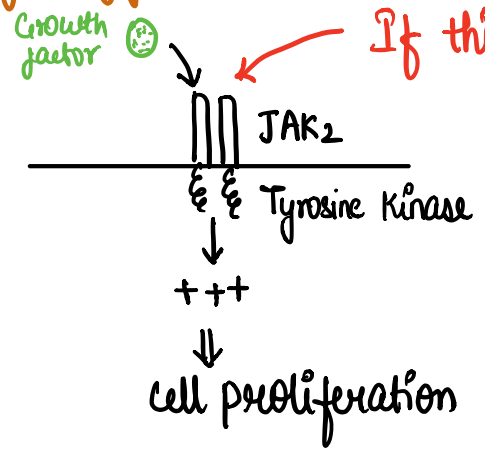
Polycythemia	EPO	Plasma	RBC	SPO_2	Etiology
① Relative	Ⓝ	↓↓	↑	Ⓝ	Dehydration
② Absolute					
1°	2° ↓	↑	↑↑↑ 1°	Ⓝ	JAK2
2°					
↳ Appropriate	2° ↑	Ⓝ	↑↑ 3°	↓ 1°	High altitude / Pulm. cardiac disease (ILD / COPD / Smoking / Long term CO exposure)
↳ Inappropriate	↑↑	Ⓝ	↑ 2°	Ⓝ	-PNS (Paraneoplastic Synd.) of RCC / HCC - PCKD

Pathology :

Ⓝ Physiology -



If this JAK_2 pathway occurs even c̄ GF, d/t JAK2 mutations,
⇓
PV / ET

C/f :

① Vasomotor symptoms

a) d/t ↑ viscosity → Shortness of Birth
(↑ viscosity is d/t ↑ erythropoiesis)
CXR infiltrates
Dizziness
Headache
Blurring of vision / Tinnitus

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b) Thrombosis – d/t ↑ Platelets, ↑ viscosity } ⇒ Risk factors ⇓ ↑ WBC count (single most important Risk factor)
↓
Both arterial & venous

c) Erythromelalgia – severe pain, – severe burning sensation, – Redness } in the involved area
↓
d/t thrombosis of end vessels / small vessels

d) Bleeding – d/t ↓ Platelet function

e) Others – Pruritis, Peptic ulcers } – d/t ↑ Histamine
Gout (d/t ↑ uric acid) → d/t ↑ cell turnover

f) Hepatosplenomegaly – common

Δ: (WHO criteria) [PS – N]

① Major Criteria:

① Hb/Hct –

	Hb	Hct
♂	> 16.5	> 49%
♀	> 16	> 48%

② BM Bx – ↑ cellularity + trilineage hyperplasia

③ JAK 2 – '+ve' → 95% – V617F
5% – EXON 12

② Minor Criteria:

① ↓ Sr. EPO

③ Others:

① ↑ Uric acid, ② ↑ LDH } d/t ↑ cell turnover
③ ↓ ESR (In Anemia, ESR ↑)
④ ↑ Sr. Vit B_{12}
⑤ ↓ Sr. Fe
⑥ ↑ LAP
⑦ ↑ PMN
⑧ ↑ Basophils
⑨ ↑ Platelets

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Rx :

① All cases –

① low dose Aspirin

② Phlebotomy

⇓

Target – (HCt)

♂ – <45%

Non-preg. ♀ – <42%

Preg. ♀ – <37%

② Selected cases :

① **Drugs** –

a) Hydroxyurea

b) Ruxolitinib (JAK1/2⊖) → used when there is intolerance/ ↓ response c̄ Hydroxyurea

c) Pegylated IFNα

↓

preferred in
- young people
- pregnant ♀

Indications of Drugs :

① ↑ thrombotic risk (age ≥ 60 yrs / H/o thrombosis)

② ↑↑↑ Platelets (>15 l)

③ Target HCt is not reached by Phlebotomy

Risk of transformation :

PV → 10-20% → PMF (>10 yrs)

PV → 2-5% → 2° AML

Prognostic factors :

a) Age → ↑ age → Poor Prognosis → ↓ survival

b) WBC count → ↑ WBC count → Poor Prog. → ↓ survival

ESSENTIAL THROMBOCYTOSIS :

Thrombocytosis

1° → Myeloid Progenitors ↓ ↑ differentiation to Megakaryocytes & Platelets
- ① ET
- ② Other MPN
- ③ MDS

2° (Reactive)
- ① Inflammation (RA/IBD/ vasculitis)
- ② Infection
- ③ Acute bleeding
- ④ Post-splenectomy
- ⑤ Neoplasms (HL)
- ⑥ Fe def.

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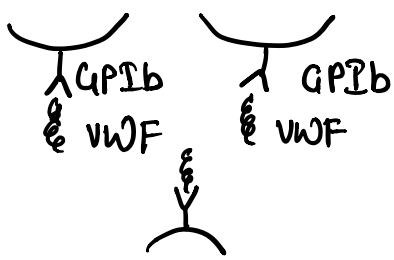
C/f:

→ similar to P.V
① Thrombosis
② Erythromelalgia

① Bleeding [acquired vWD]



→ ↓ free vWF in blood because they are attached to platelets

Δ:

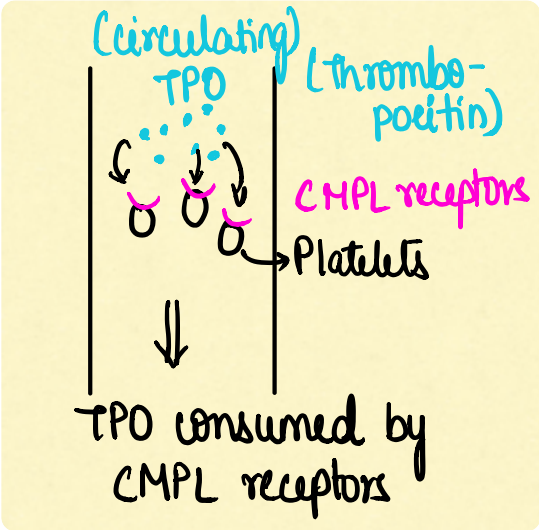
① PS – large hypogranular platelets
– Platelet clumps

② BM – Megakaryocyte hyperplasia
– to rule out
a) IDA [BM Fe stores ↓]
b) Pre PMF [atypical megakaryocytes]
c) MDS

[BM is not needed in PV, but very much needed in ET]

Mutations:

① JAK 2 – V617F (60-75%)
② CALR – 20-25%
③ CMPL – 5%
④ Triple negative – 5-10%



Negative feedback of Platelets:

↑ Plt.
↓
↑ consumption of TPO by CMPL
↓
↓ TPO
↓
↓ Plt.

↓ Plt
↓
↓ consumption of TPO by CMPL
↓
↑ TPO
↓
↑ Plt

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→ rule out other MPN/MDS
↓
CML
P.V
PMF

Rx :

① Low risk :

- Optional Aspirin (used when there are vasomotor symptoms)

② High risk :

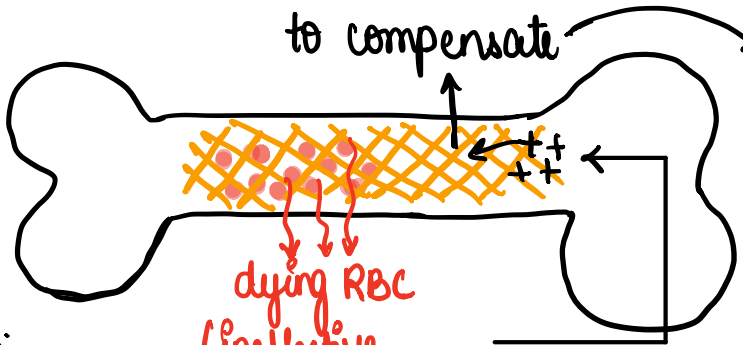
Age ≥ 60
H/o thrombosis
Platelets >> 15L
} → ① Aspirin + Cytoreduction
Hydroxyurea / Pegylated IFNα

② Anagrelide (PDE2 ⊖)
MOA – ↓ differentiation of Megakaryocytes to Platelets

Risk of Transformation :

ET
20% → PMF
< 2% → 2° AML

PRIMARY MYELOFIBROSIS :



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→ Massive Splenomegaly → ① in PV & ET → d/t ↑ sequestration of ↑ cells
② in ET → d/t EMH

→ Bone Marrow → ↑ work
↓
↑ cell turnover → ↑ LDH
fatigue
wt. loss
night sweats

→ RBC when trapped b/w the fibres ↓
ab(n) shapes → Tear Drop RBC

Classification :

Myelofibrosis → Other
- ① CML
- ② AML (M7)
- ③ ALL
- ④ MDS

d/t high PDGF production

- ⑤ Solid organ cancers (Breast / Prostate)
- ⑥ Autoimmune (SLE)
- ⑦ Toxins (Benzene)
- ⑧ Granulomas (TB/ Sarcoidosis)
- ⑨ Gaucher's

↓
1° (PMF)
- Primarily
- Post-PV
  Post-ET
  (Spent phase)

C/f & Δ :

① PS :

① Anemia
② WBC / Platelets (variable) (large platelets)
③ ↑ Platelets in [Pre-PMF] – only thrombocytosis seen
± atypical megakaryocytes in BM
④ Leuko-Erythro-Blastic reaction
→ Tear drop RBC + Precursors of leuko & erythroid lineages in blood

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② BM Aspiration:

① Dry Tap → So, BM Biopsy is taken

Pre-PMF

- Atypical megakaryocytes
- ↑ megakaryocyte proliferation
- Grade 1 reticulin deposition
- ↑ cellularity

late fibrosis

→ marked megakaryocyte
→ Atypia
→ Grade 2/3 Reticulin deposition / fibrosis

Mutations:

① JAK2-V617F → 45-60%
② CALR → 30-40%
③ CMPL → 7-10%
④ Triple -ve → 2%

Prognostic factors:

① Age >65 — ①
② Constant symptoms — ①
③ Blasts (Blood) >1% — ①
④ WBC >25,000 — ①
⑤ Hb <10g% — ①

0 — low risk
1-2 — Intermediate risk
≥3 — High risk

Rx:

① Asymptomatic
No poor prognostic factors } ⇒ NO Rx

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② Symptomatic: (or Poor prognostic factors) → Rx – ① Ruxolitinib (JAK 1/2 ⊖)

② Other JAK1/2 ⊖:
- Pacritinib
- Momelotinib
- Fedratinib

③ Androgens / Lenalidomide

④ Hydroxyurea – if there is significant ↑ WBC / ↑ Platelet

Alternative Rx:

① Splenectomy – Indications –
- a) Transfusion dependent anemia
- b) Massive Splenomegaly → causing abd. pain (left hypochondriac pain)

② ESA – can be used in case of
- a) Refractory anemia
- b) when EPO levels < 500

* But, ESA worsens Splenomegaly in case of PMF

③ Allogenic HSCT can also be done

	PV	ET	PMF
Defect	– ↑ RBC	– ↑ Platelets	– Anemia (↑MCV)
C/f	– thrombosis / erythromelalgia / Bleeding /	– similar to PV	– ↑ TC / ↑ Platelets / Massive Splenomegaly
Mutation	– JAK2	– JAK2 / CALR / CMPL	– JAK2 (m/c) / CALR / CMPL
PS	– (N)	– Large hypogranular	– leukoerythroblastic reaction
BM	– Trilineage hyperplasia	– megakaryocyte hyperplasia	– Fibrosis – Megakaryocyte atypia

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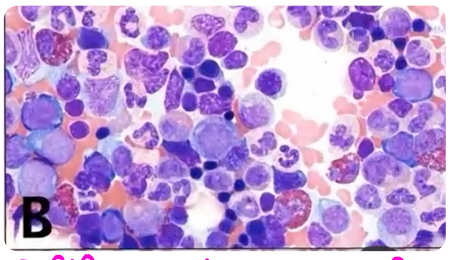
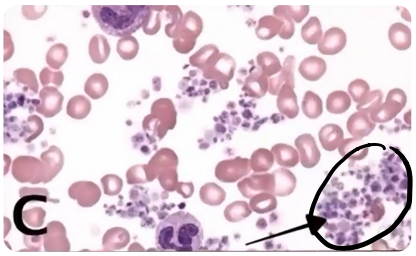
Erythromelalgia

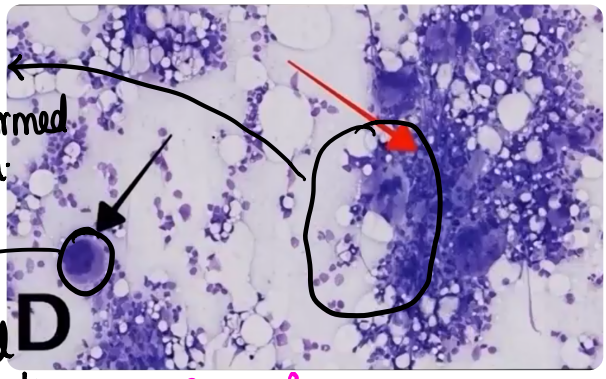


Trilineage hyperplasia (PV)

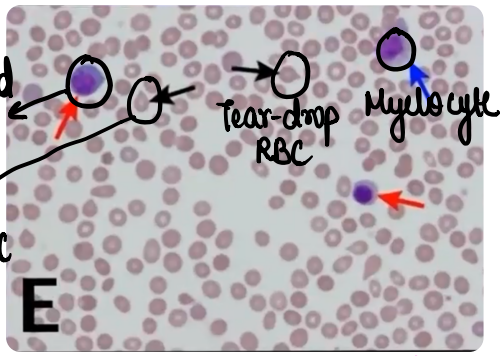


Platelet clumps (ET)

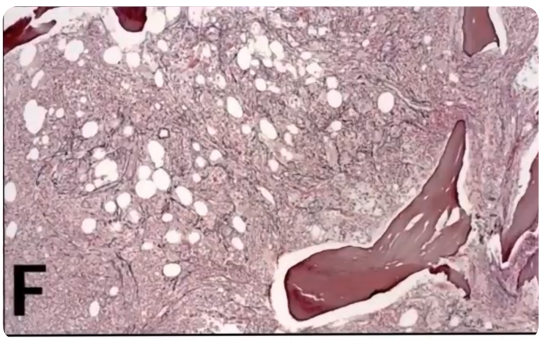
- EDTA induced platelet clumps → Thrombocytopenia
- ET induced clumps → Thrombocytosis



BM Biopsy



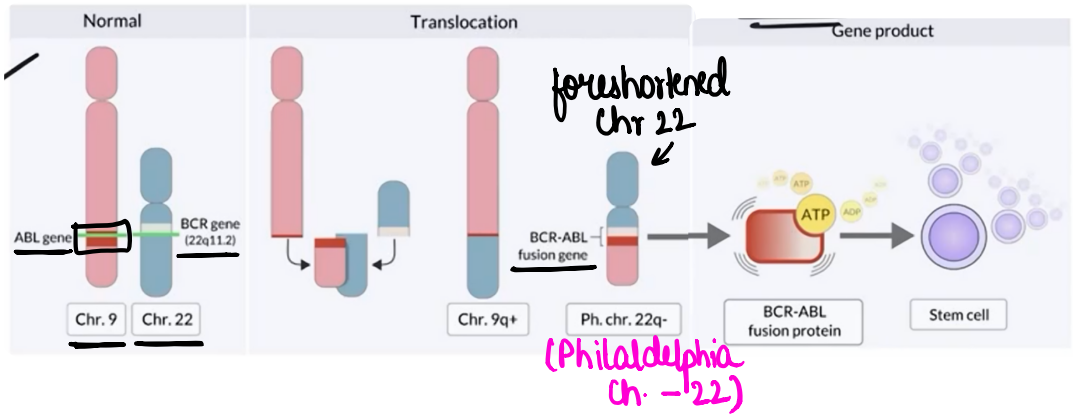
Leukoerythroblastic reaction



Fibrosis of BM on Reticulin staining

Myeloproliferative Disorders - 2

CHRONIC MYELOID LEUKEMIA :



⇒ Philadelphia chromosome
- t(9;22)
- BCR-ABL translocation

Myeloid Precursor
- Granulocyte
  - → Eosinophil, Basophil
  - → CFU-G → Neutrophils
- Erythrocytes
- Megakaryocytes

++++ ABL Kinase (very imp.)

Phelaldelphia Chr. (BCR-ABL fusion kinase) (more aggressive)

→ Usually Chr 9 has ABL gene → codes for ABL Kinase (145 KDa) ↓ Ⓝ size

→ But, BCR-ABL fusion protein (↑ Kinase activity)
- 210 KDa (m/c)
- 190 KDa (less common)

End result of this fusion ⇒ ↑ Neutrophilic precursors + ↑ Neutrophils

Epidemiology :
- 68 yrs
- 10-15% of Adult leukemia
- ↑ risk c̄ Radiotherapy
- no relation c̄ drugs / cytotoxic drugs

m/c adult leukemia is CLL

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* AML – a/w RT & CT
  CML – a/w only ~~C~~ RT
  CLL – not a/w any of the both

CLASSICATION : [85% of cases have this kind of evolution.

	CHRONIC PHASE	ACCELERATED PHASE	BLASTIC PHASE
Blasts (BM)	<10%	10 – 19%	≥ 20%
Association	– ⟷ – Asymptomatic + Splenomegaly – may have constitutional symptoms	– ↑↑ Basophils (≥20%) – Platelets < 1,00,000 – Clonal Evolution (new changes) – Megakaryocyte proliferation & fibrosis	[2/3 – Myeloid Blasts 1/3 – Lymphoid Blasts]

* When moving from one phase to another, symptoms may worsen.

Diagnosis :

① PS – Leukocytosis ⇒ Left Shift + All stages of myeloid maturation
± Basophilia
± Thrombocytosis (talks about accelerated phase)
± Anemia (d/t ↓ erythroid lineage synthesis)
later may become thrombocytopenia

② BM – Hypercellular
↑ M:E ratio

③ Karyotyping – Philadelphia Chromosome '+ve'
[BCR- ABL fusion]

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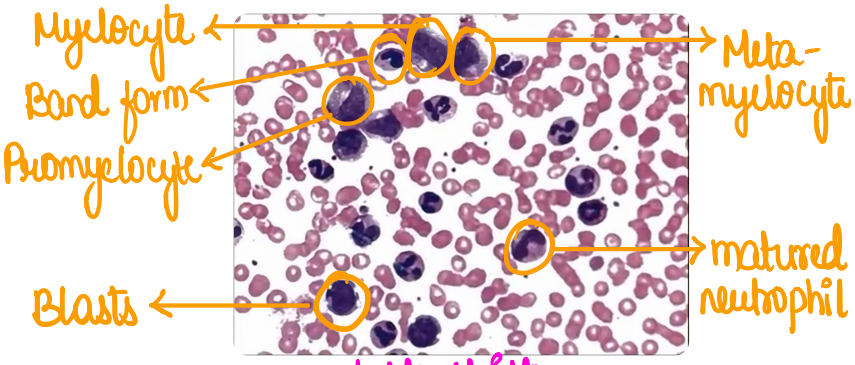


Left shift

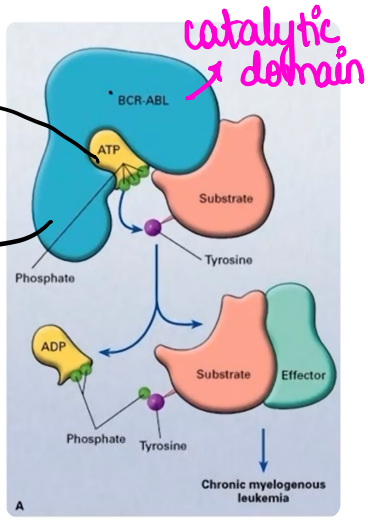
Karyotype - t(9;22)

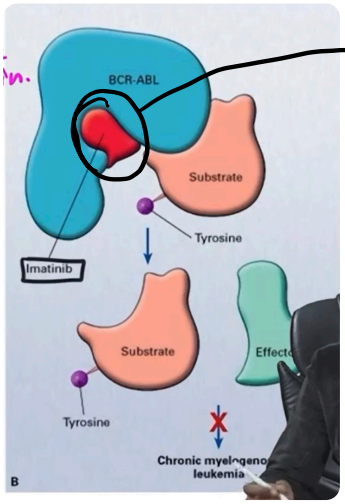
Rx :

① 1st line :

① TKI (Tyrosine Kinase Inhibitors) ⇒ IMATINIB [Gold std.]

→ ⊖ BCR-ABL Kinase





→ Once ATP is bound to BCR-ABL, tyrosine is phosphorylated ⇒ CML

→ Imatinib binds to the ATP binding site of BCR-ABL ⇒ substrate will not get phosphorylated ⇒ no CML

TKIs :

1st gen. - Imatinib ⇒ S/E - a) Nausea & Vomiting
b) Diarrhoea
c) Cramps
d) Cytopenias
e) ↓ PO_4
f) ↑ QT
g) CHF

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② 2nd gen – ↑ Potency
↑ Toxicity

① NILOTINIB	② DASATINIB	③ BASUTINIB
↑ QT	Effusions	Rash
↑ Bilirubin	↑ QT	Diarrhoea
↑ lipase	Pulm. HTN	↑↑ SGOT/SGPT
CV toxicity		[no QT↑]

* The only TKI which doesn't cause ↑QT ⇒ Bosutinib

Resistance to Imatinib → by undergoing Clonal evolution
↓
BCR-ABL Kinase mutations
[eg: T3151 mutations]
↓
– mutation of ATP binding site
– Deadly mutation
– no TKI are effective, except Ponatinib [most effective drug for T3151]
↓
S/E – Pancreatitis
↑ Thrombotic complications

Drugs for T3151 mutations
↓
Ponatinib
Omcetaxine
Asciminib

Imatinib Resistent Disease
↓
T3151 mutations
Yes → Ponatinib
No → Other 2nd Gen. TKI's

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→ TKIs are contraindicated in Pregnancy. [Even hydroxyurea is C/I. IFN α only can be gi

DEFINITIONS: [Milestones!]

Complete Hematological Response (PS)

1. Platelets < 4.5 l
2. WBC < 10,000
3. Spleen – (N)
4. DC – (N)
   ↓
   Basophils < 5%

Cytogenetic Response (CR) (FISH)

1. No response – Ph. > 95%
2. Minimal " – 66–95%
3. Minor " – 36–65%
4. Partial " – 0%
5. Complete Cytogenetic Response (CCyR)
   ⇓
   Ph. – 0%

Molecular Response (RT-PCR)

1. Major (MMOR) – BCR-ABL transcripts < 0.1% [>3 log reduction]
2. Complete (undetectable) – BCR-ABL transcripts 0% [>4 log reduction]

MILESTONES:

	Optimal Response	Suboptimal	Failure
3 months	BCR-ABL (>1 log red) <10%	< Complete Hematological response	No hematological response
6 months	– BCR-ABL < 1% (2 log red) – Ph. < 35% (Partial response)	Ph > 35% (< Partial response)	Ph > 95%
12 months	– CCyR (Ph – 0%) – MMOR [BCR-ABL < 0.1% (or) > 3 log red]	Ph 1–35%	Ph > 35%
Anytime after 12 months	–	→ loss of MMOR – BCR-ABL > 0.1% – Molecular recurrence	– Detectable Ph ch. [absence of CCyR]

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→ In case of Molecular recurrence / absence of CCyR (after using Imatinib)

↓

Shift to 2nd gen TKI
+ Check for T315I mutations

Yes → Ponatinib

No → Continue c̄ 2nd gen. TKI

↓

Suboptimal / failure

↓

Allogenic HSCT

Discontinuation of TKI:

→ When? – ① Complete molecular response > 2 yrs

Allogenic HSCT:

→ If Pt. presents c̄ Acceleration Phase / Blast Phase, give Allogenic HSCT as 1st line of Rx

→ ≥2 TKI failure / Suboptimal response

CHRONIC NEUTROPHILIC LEUKEMIA:

→ CSF3R mutations

→ Clonal defect ------> Evolution ------> Transforms into AML (1 yr)

Features – ↑ PMN + no Etiological causes + no ↑ Blasts / Immune cells

↓

+ Anemia
+ Thrombocytopenia
+ Mild splenomegaly

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→ BM – M:E = 20:1

→ Rx – Hydroxyurea (or) IFNα
± Allogenic HSCT

CHRONIC EOSINOPHILIC LEUKEMIA:

→ PGFR-A ↔ FIP1L1 mutation (Chr 4)

→ Chronic Eosinophilia (Eosinophils >1500) ⇐ PS + in BM

Blasts – 5-20%
↓
CD23/CD25/CD69 '+ve'

→ Infiltration of organs → ① Heart – Endo Myocardial fibrosis
– Restrictive Cardiomyopathy
② lungs
③ Skin
④ GIT

→ May transform into AML

→ Rx – Imatinib can be used

Hyper Eosinophilic Synd.	Chronic Eosinophilic Leukemia
Eosinophils > 1500	Eosinophils > 1500
No etiology	No etiology
Multi organ dysfunction	Multi organ dysfunction
Blasts < 5%	Blasts – 5-20%
Clonality ⊖	Clonality ⊕

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OTHER MUTATIONS :

GIST tumors also respond to Imatinib

① PDGRB ⟷ ETV6 fusion :

→ CMML ± Eosinophilia

→ C/f – Skin manifestations
Splenomegaly

Rx – Imatinib

② FGFR1 Rearrangement : (8p Syndrome)

[doesn't respond to Imatinib]

→ Stem cell syndrome

→ C/f – 'B' symptoms
Splenomegaly
Leukocytosis
Lymphadenopathy

Rx – only HSCT

Myelo Dysplastic Syndrome

MYELODYSPLASTIC SYNDROME:

Patho – Myeloid progenitor [Monoclonal defect]

↓

defective differentiation & maturation

⇓

Dysplastic cells [Key feature]

- ↑ apoptosis in BM → Cytopenias → ↑ Haematopoiesis in BM → Hypercellular BM
- Peripheral Blood (Dysplastic)

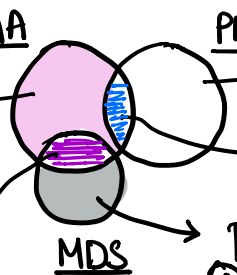
* No Splenomegaly in MDS

Hallmarks of MDS:

1. Dysplastic cells *
2. Cytopenias *
3. Hyperplastic BM (Optional)

Hypoplastic MDS:

→ MDS overlapped c̄ Aplastic Anemia / PNH



1. no dysplasia (hypocellular marrow)
2. Hypoplastic MDS (Hypocellular marrow + Dysplasia) [MDS overlap c̄ AA]
3. Dysplasia + hypercellular marrow
4. PNH clone + hypocellular marrow [MDS overlap c̄ PNH]
5. PNH clone + cellular marrow

All of them show Pancytopenia [acquired stem cell defect]

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Etiology:

MDS

- **1° MDS** (90%) (elderly – 70yrs)
- **2° MDS** (10%) →
  1. Post chemoRx [Treatment Related MDS]
     - Alkylating agents
     - Topoisomerase ⊖
     - Azathioprine
  2. Benzene
  3. Radio Rx
  4. PNH

Mutations: [Epigenetic Changes]

1. DNA methylation [DNMT 3A / TET2 / IDH 1/2]
2. Histone modification [ASXL1 / EZH2]
3. RNA splicing [SFSB1] → Specific for MDS
4. Others – RUNX1 ; NRAS / KRAS (for Signal transduction)
   TP53 ; STAG2 (cohesion complex for mitosis)

(remaining are non-specific & can be found in AML & MDS)

* AML only – NPM1
FLT 3

Clinical features →

1. Anemia (m/c) (75%) – Macrocytic
2. Neutropenia (50%) ⇒ Infections are out of proportion to neutropenia
3. ↓ Platelets (50%)
4. NO splenomegaly

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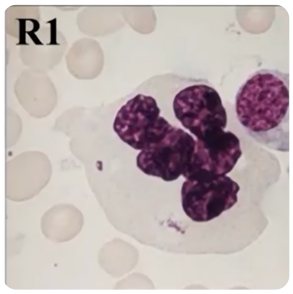
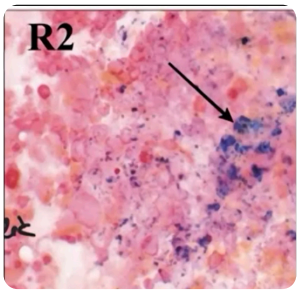
Δ: ① PS – Dysplasia ± Megaloblastic changes
② BM – ≥10% dysplasia + Blasts
↓
m/c < 5% [upto 19% possible]
[if >20%, Δ goes towards acute leukemia]
[>5% ⇒ In, MDS c̄ excess blasts]

DYSPLASTIC CHANGES:



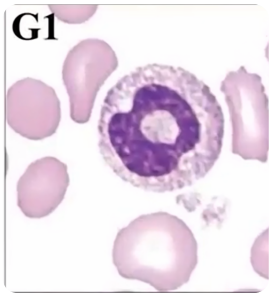
① Multinuclear Polychromatophilic erythroblast



② Fe Overload (Pearls Prussian Blue stain – BM)

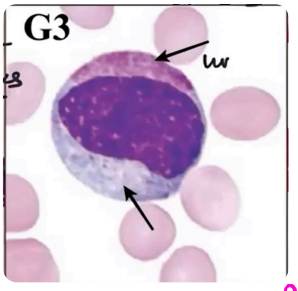
③ RBC – nuclear Bridging

④ Ringed Sideroblasts
[⑤ ± uneven cytoplasmic staining
⑥ ± oval macrocytes]

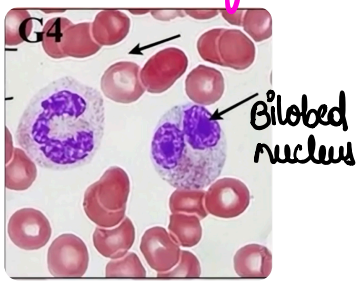


Bizarre nucleus (Donut / Ring shaped nucleus)

Agranular Monocytoid Neutrophil (Neutrophil ∄ granules)

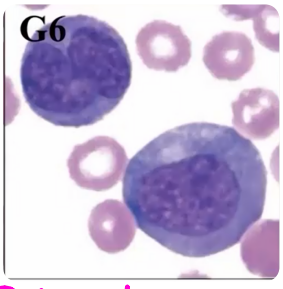


Uneven cytoplasmic staining

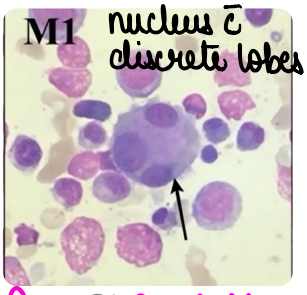


Pseudo Pelger Heut (Pelger Heut anomaly d/t MDS)

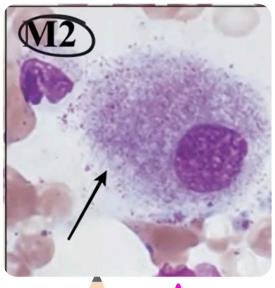
Hypersegmented PMN



Intensely Basophilic Cytoplasm



Pawn Ball Mega-Karyocyte



Mononuclear megakaryocyte

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CLASSIFATION OF MDS:

2015 Classification	2008 classification	PS findings	BM findings
① MDS - SLD (Single lineage dysplasia)	① MCUD (Multilineage Cytopenia c̄ Unilineage Dysplasia) a) Refractory Anemia b) " Neutropenia c) " Thrombocytopenia	- ≥ 2 lineages cytopenia - < 1% blasts (≈ no)	- 1 lineage dysplasia - < 5% Blasts - Auer rods -ve - ≤ 15% Ringed Sideroblasts (RS)
② MDS - MLD (Multilineage Dysplasia)	② Refractory Cytopenia Multilineage Dysplasia (RCMD)	→ 1-3 lineages cytopenia → < 1% blasts	→ 2-3 lineages dysplasia → < 5% blasts → Auer rods -ve → ≤ 15% RS
③ MDS - RS (MDS c̄ Ringed Sideroblasts)	③ Refractory anemia c̄ Ringed Sideroblasts	→ Anemia → < 1% blasts	→ Erythroid dysplasia → < 5% blasts → Auer rods -ve → > 15% RS
④ MDS c̄ isolated 5q deletion	④ 5q deletion	→ Anemia → Thrombocytosis → < 1% blasts → common in ♀	→ Ⓝ / ↑ megakaryocytes (dysplastic) → < 5% blasts → Auer rods -ve
⑤ MDS c̄ EB (excess Blasts)	⑤ (i) RAEB-1 (Refractory Anemia c̄ Excess Blasts)	→ Cytopenia → 2-4% Blasts	→ Dysplasia (≥1) → 5-9% blasts → Auer rods -ve
	(ii) RAEB-2	→ Cytopenia → 5-19% Blasts	→ Dysplasia (≥1) → 10-19% Blasts → Auer rods -ve
⑥ Unclassifiable	⑥ MDS-U (Unclassified)	→ Cytopenia → < 1% Blasts	→ Unilineage dysplasia → < 5% Blasts

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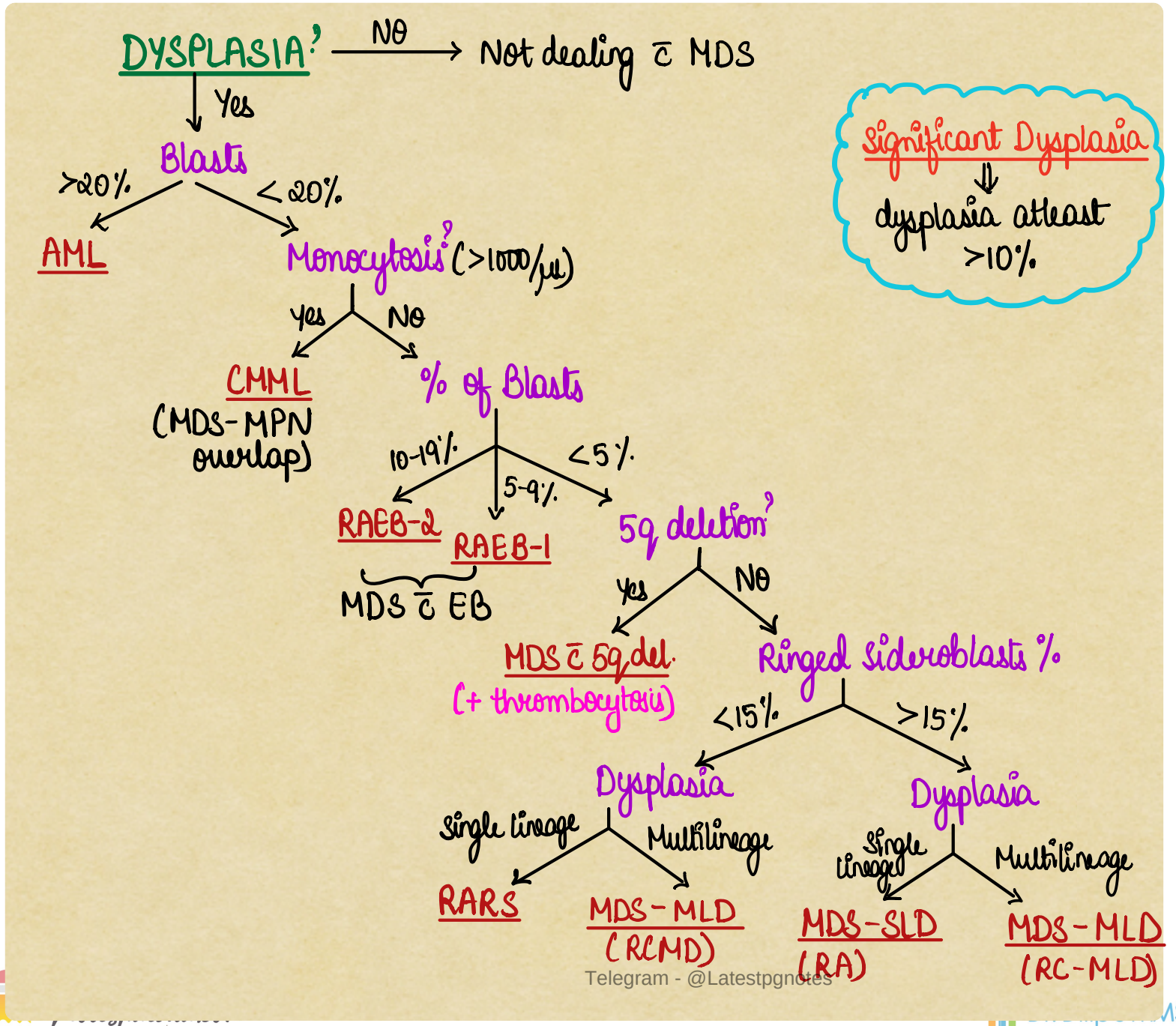
Additional Points:

① If Blasts >20% – Acute leukemia

② Monocytes >1000 + Dysplasia ⟹ Overlap [CMML & JMML to be differentiated]

Other conditions c̄ Dysplasia:

① B_{12} / folate def.
② Cu def.
③ HIV
④ Chemo Rx
⑤ Alcohol
⑥ Heavy metals (lead/Arsenic)



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CYTOGENETICS:

① Very good Prognosis → Y deletion / 11q deletion
② Good Prognosis → Ⓝ Cytogenetics [5q / 20q / 12p deletions]
③ Intermediate Prognosis → Double Dependent Clones
④ Poor Prognosis → 7q deletion / Inversion (3) / 3q deletion
⑤ Very Poor Prognosis → Complex (> 3 abnormalities)

SCORING SYSTEMS:

① International Prognostic Scoring System: [IPSS]

Components –

① Marrow blasts
② Cytogenetics
③ Hb
④ Platelets
⑤ Absolute Neutrophil Count

Score –

≤ 1.5 – very low risk
1.5 - 3 – low risk
3 - 4.5 – intermediate risk
4.5 - 6 – high risk
> 6 – very high risk

TREATMENT:

① Poor Performance MDS

① Supportive Rx:
a) ESA
b) G-CSF [Algastrim
↑ risk of splenic rupture MDS]
c) TPO mimetics
② ± Antibiotics
③ ± Fe Chelation

② Good Performance MDS:

Low / Intermediate risk
↓
① Lenalidomide (for 5q syndrome)
② DNA Hypomethylating agents [Azacitidine / Decitabine] for TET2 mutations
③ + Supportive measures

Intermediate to high risk
↓
① Allogenic HSCT (fit pts.
② DNA hypo-methylating agents (unfit pts.)

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③ Hypoplastic MDS : [MDS overlap c̄ Aplastic Anemia]

Rx – Immunosuppressants ± HSCT
[Cyclosporine / ATG / Steroids]

MDS-MPN OVERLAP :

CMML

① Chronic MyeloMonocytic Leukemia
② Monocytosis > 1000/μl (PS)
③ Myeloblasts < 20% (BM)
④ Dysplasia ✓

C/f – a) Skin rash
b) Gum Hypertrophy
c) Splenomegaly

⑤ Rule out –
a) BCR-ABL transformation
b) PDGFR A/B "
c) FGFR 1 "

⑥ Rx – Allogenic HSCT
⑦ will not respond to Imatinib

JMML

① Juvenile Myelo Monocytic Leukemia
② Monocytosis > 1000/μl (PS)
③ Myeloblasts < 20% (BM)
④ Dysplasia ✓

C/f – a) Age < 4yrs
b) + Skin rash (Eczematous)
c) + Lymphadenopathy
d) + Hepatosplenomegaly

⑤ a/w – a) NF-1
b) Noonan synd. [PTPN 11]
c) Monosomy 8 (common)

⑥ Rx – Allogenic HSCT
⑦ will not respond to Imatinib

* PDGFR A → l/t Chronic Eosinophilic leukemia
* PDGFRB → l/t CMML c̄ excess eosinophilia
* FGFR1 → l/t 8P stem cell syndrome

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Basics of Haemostasis - 1

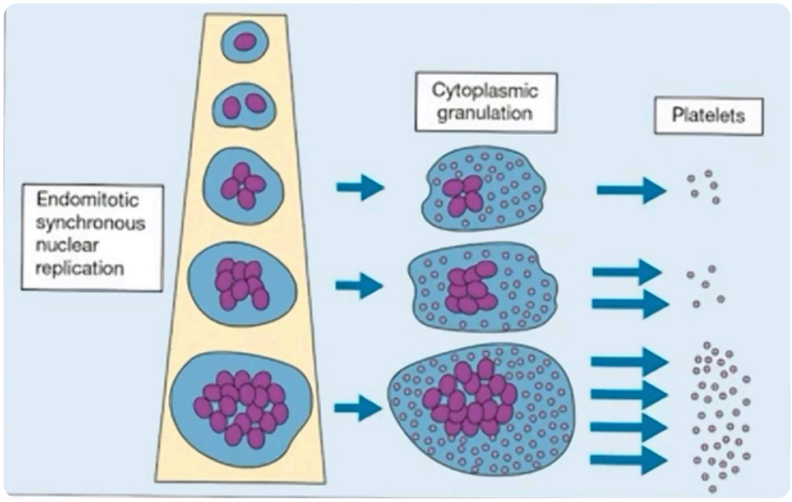
PLATELETS :

Formation :

Hematopoietic Stem Cell → Common Myeloid Progenitor → Megakaryoblast → Megakaryocyte → Platelets

* 1 Megakaryocyte gives 1000 - 5000 Platelets

→ Time taken for formation of Platelets = 10 days

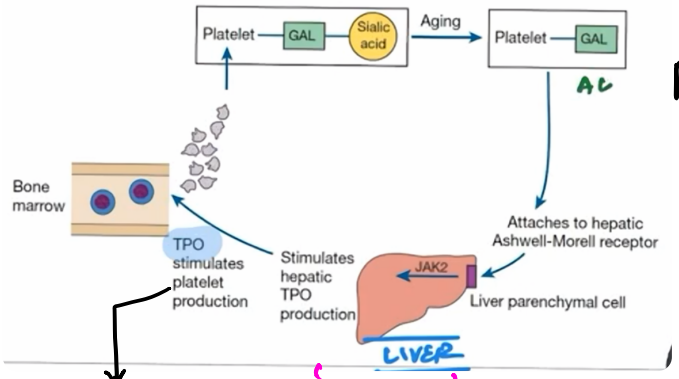


Endomitotic replication :

→ only nucleus replicates (doesn't divide, only replicates)

→ then, finally, cytoplasm is divided among all the formed nuclei & platelets are formed

Regulation -



Aged platelets lose Sialic acid
↓
Attach to hepatic Ashwell-Morell Receptor
↓
+++ Hepatic Thrombopoietin (TPO) production
↓
TPO stimulates BM to produce more platelets

Regulated by 'C-MPL' receptors on Platelets

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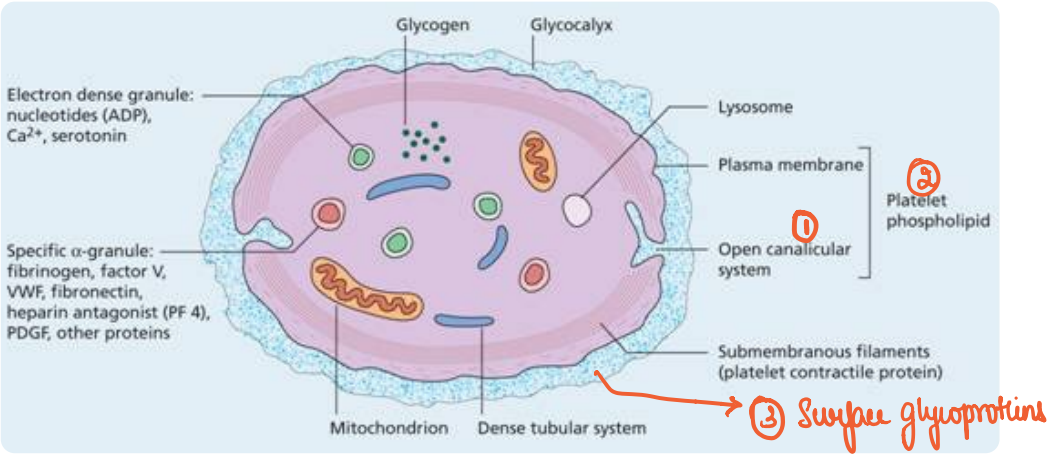
PARTS OF PLATELETS :



① **Open Canalicular System** – Invagination through which all the storage granules move out.

② **Platelet Phospholipid** – activates Clotting factors (X / II) ⇒ Xa / IIa
– Includes Plasma membrane & open canalicular system.

③ **Surface Glycoproteins** –

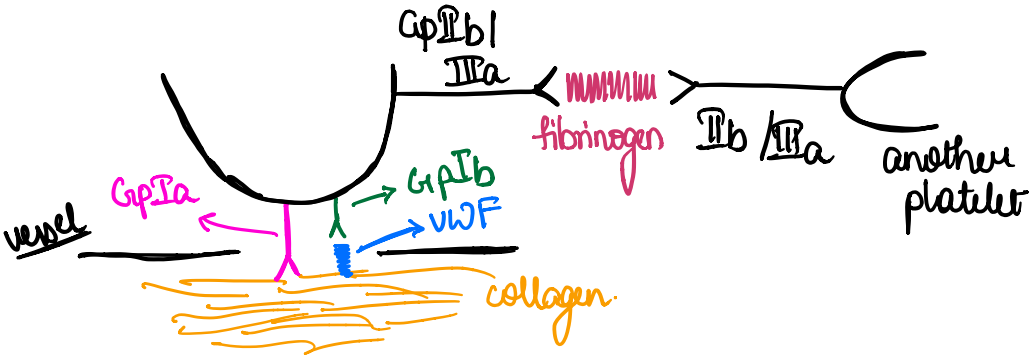
Adhesion

① GpIa [$\alpha_2\beta_1$ integrin CD 42] → attaches to Collagen

② GpIb [GpIb (V/IX)] → attaches to VWF

Aggregation

① GpIIb / IIIA ($\alpha_2\beta_3$ integrin)
[major ligand → Fibrinogen
minor ligand → vWF]



Adhesion ⟶ ++ Activation of GpIIb/IIIA ⟶ Aggregation

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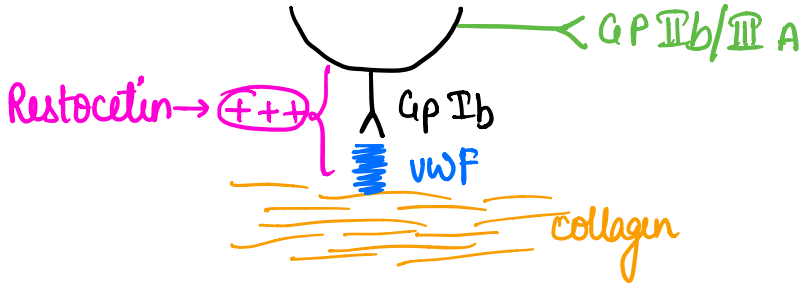
Defects a/w Surface Glycoproteins :

① **Bernard Soulier Syndrome** → [Adhesion effect]

→ defect in Gp Ib
→ Autosomal recessive
→ Bleeding
→ Giant Platelets → in P.S
→ Aggregation tests → abnormal
[Restocetin test - ↓]

② **Glanzmann thrombasthenia** → [Aggregation defect]

→ Autosomal Recessive ; defect in Gp II b/III a
→ Bleeding
→ All aggregation tests → abnormal [except Restocetin test]



So, defect in GP IIb/IIIa will not affect Ristocetin test.

④ **Storage Granules :**

① **Delta granules** → electron dense granules [made of nucleotides (ADP), Ca^{+2}, Serotonin]

② **α - granules** → made of fibrinogen, factor V, vWF, fibronectin, heparin antagonist (PF-4), PDGF, other proteins.

③ **Lysosomes**

Defects in Storage :

① **Delta Storage Pool disease** → defect in Delta granules

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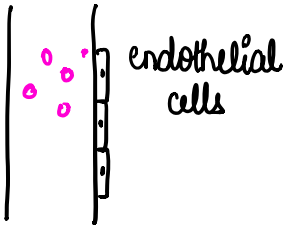
② Grey Platelet Syndrome → defect in α-granules
- → Autosomal Recessive
- → GPIIb gene mutation
- → ↓ Platelets (thrombocytopenia) & bleeding
- → Giant Platelets [Peripheral smear]
- → PDGF ↓↓ in platelets ⟹ ↑↑ PDGF in BM (Bone marrow) ⇒ Rapid Myelofibrosis (B.M fibrosis)

* Circulating Platelets do not get adhered to endothelium d/t selective activation of selective enzymes in certain places

ACTIVATION OF PLATELETS :



Arachidonic Acid
↓ COX
PGH intermediates

[in Endothelium] → ++ Nitric Oxide → ⊕ { ↓ Platelet adhesion, Vasodilatation

[in Endothelium] → PGI_2 (Prostacyclin) ⇓ ↓ Platelet adhesion

[in activated Platelets] → TXA_2 (Thromboxane) ⇓ ↑ Platelet adhesion, Vasoconstriction

$$\Rightarrow \frac{PGI_2}{TXA_2} \Rightarrow >1 \quad (\uparrow\uparrow PGI_2)$$

Endothelial injury } ——— ++ Platelets ——→ $\frac{\cancel{PGI_2}}{TXA_2 \uparrow\uparrow} \Rightarrow <1 \Rightarrow$ Platelet aggregation, Vasoconstriction

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① Primary Activation:

Reasons – ① ↓ PGI2 / ↓ NO

② Platelet Binding c̄ — a) GpIa [collagen]
b) GpIb [VWF → Collagen]
c) PAR 1/4 [Thrombin]
(Protease Activation Receptor)

[Thrombin comes initially from extrinsic pathway & later from intrinsic pathway]

⇓

↑ Granule release } [ADP]
++ GpIIb/IIIa }

[ADP – both autocrine & paracrine function
⇓
activates both the platelet from which it is released & also other nearby platelets]

[ADP receptors – P_2Y_1
P_2Y_{12}]

Function of ADP:

ADP

P_2Y_1
↓
Gq receptor
↓
↑ Phospholipase C
↓
↑ IP_3 + DAG
↓ ↓
↑ Ca^{+2} ↑ Phosphokinase C

P_2Y_{12}
↓
G_i Pathway
↓
↓ CAMP
↓
↑ Intracellular Ca^{+2}

↑ granule release
+++ TXA_2 synthase
↑ GpIIb/IIIa

↑↑ TXA_2

② Secondary Activation

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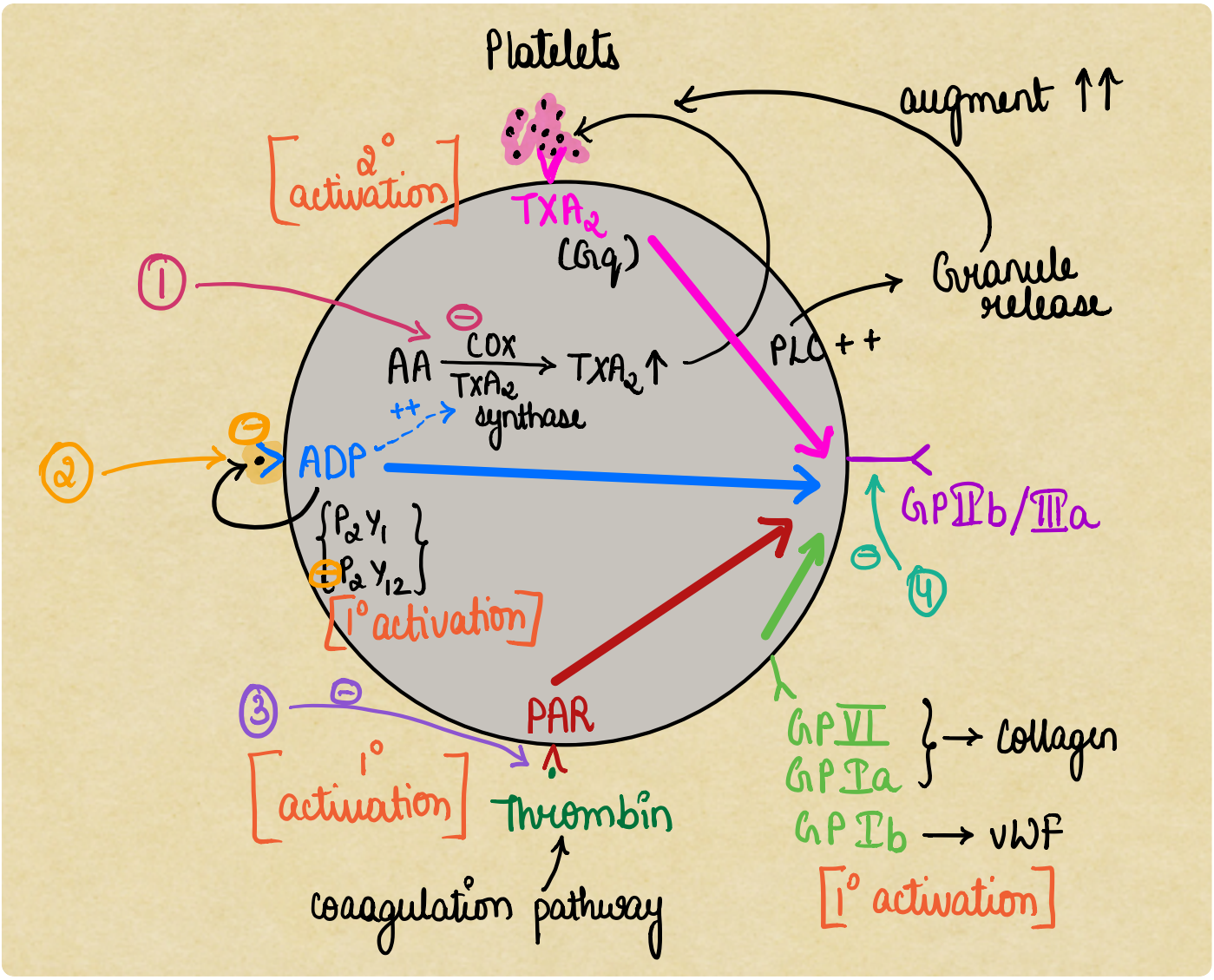
↑↑ TXA_2
↓
⊕ Gq receptor
↓
↑ Phospholipase C ⟶ [IP_3 + DAG] ⟹ ↑↑ Granule Release
++ GPIIb/IIIa

* Ultimately GPIIb/IIIa is augmented till a complete clot is formed.



Anti Platelet Drugs : [Aggregation ⊖]

① Aspirin
Other NSAIDs } ⟹ ⊖ COX

[Aspirin – Irreversible / Others – Reversible]

[Aspirin – acts more by ↓ Granule release
– Platelet ⊖ / Aggregation ⊖ / Adhesion ⊖

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② Clopidogrel, Prasugrel } - Oral, - Pro drugs } irreversible

MOA – ⊖ ADP receptors (especially P_2Y_{12})

Ticagrelor, Langrelor } - I.V., - Active compounds

Elinogrel – Oral / I.V.

} Reversible

③ Vorapaxar → ⊖ PAR (Protease Activation Receptor) [Reversible]

④ Abciximab [Irreversible]

Eptifibatide, Tirofiban } → ⊖ / ↓ GpIIb/IIIa [i.v.] [Reversible]

PLATELETS – VALUES :

Ⓝ count → 1.5 – 4 l /mm³

- < 1.5 l/mm³ ↓ Thrombocytopenia
- > 4 L/mm³ ↓ Thrombocytosis

Causes –

1. Fe deficiency
2. Hemolytic Anemia
3. Post-splenectomy
4. Cancer / Malignancies
   - ↳ CML (Chronic)
   - ↳ Essential thrombocytosis + other MPD
   - ↳ Pre-1° Myelofibrosis
   - ↳ 5q del. MDS
5. Infections / Inflammations

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Basics of Haemostasis

HAEMOSTASIS

Primary (1°)
(Temporary fibrin clot formed)
⇓
By Platelets

Primary
↓
GP gene, PAR " } Collagen, VWF, Thrombin

ADP --⊕--> TXA_2 Synth.
↓
↑ TXA_2 (Thromboxane)
⇓
Initiation

Secondary
↓
↑ TXA_2 (main booster for 2° activation)
⇓
Boost

↑ Granule release
↑ Gp IIb/IIIA expression
⇓
Defects in hemostatic plug formation
⇓
Bleeding disorders

Secondary (2°)
(stable fibrin clot formed)
⇓
By Clotting Factors

Extrinsic
Tissue Injury
(Initiation) ++
↓
X a → common pathway
↓
II (Prothrombin) → IIa (Thrombin) (Pico molar)
↓
Fibrinogen → Fibrin
(not much contribution)

Intrinsic ++
(Amplification)
↓
X a → common pathway
↓
IIa ← II (Billion times ↑)
IIa → Fibrin ← Fibrinogen
Fibrin → Stable clot
↓
Fibrinolytic

(Thrombin) IIa ++

⇓
Defect in Coagulation pathway
⇓
Clotting Disorders

*** Factor IIa :**
1. +++ Amplification (Intrinsic)
2. ++ Platelets (PAR)
3. +++ anti coagulation (Prot. C)
4. +++ Fibrinolytic system

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Bleeding disorders:

1. Thrombocytopenia
2. Bernard Soulier
3. Uraemia (↓ function of Platelets & there is no thrombocytopenia)
4. Glanzmann thrombasthenia
5. Storage pool disorders
6. Drugs –
   a) COX ⊖
   b) P_2Y_{12} ⊖
   c) PAR ⊖
   d) GPIIb/IIIa ⊖

   } aggregation ⊖

Clotting disorders:

1. Hemophilia A/B (VIII > IX) m/c
2. Acquired (liver / DIC)
3. Drugs –
   a) Warfarin
   b) Heparin
   c) Thrombin ⊖
   d) Factor Xa ⊖

⇓

Von Willebrand Disease

[c/f of both bleeding disorders / clotting disorders]

- Platelet glue
- F VII Binding

2° HEMOSTASIS:

Extrinsic Pathway (Initiation)

Tissue damage } → ↑ Tissue factor } → VII

↓ Ca^{+2} / Phospho lipids (Ca/PL)

VIIa

↓

X → Xa

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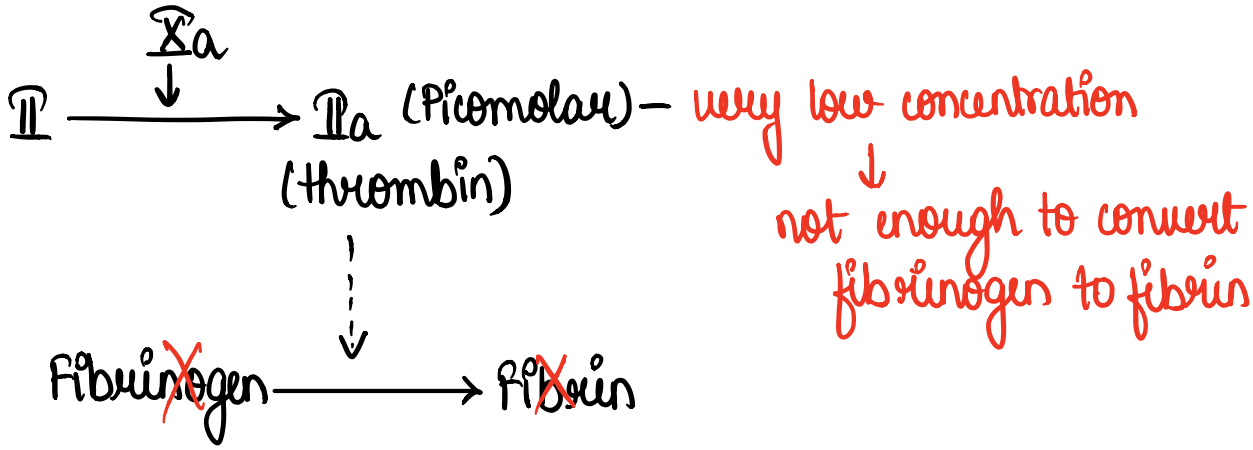
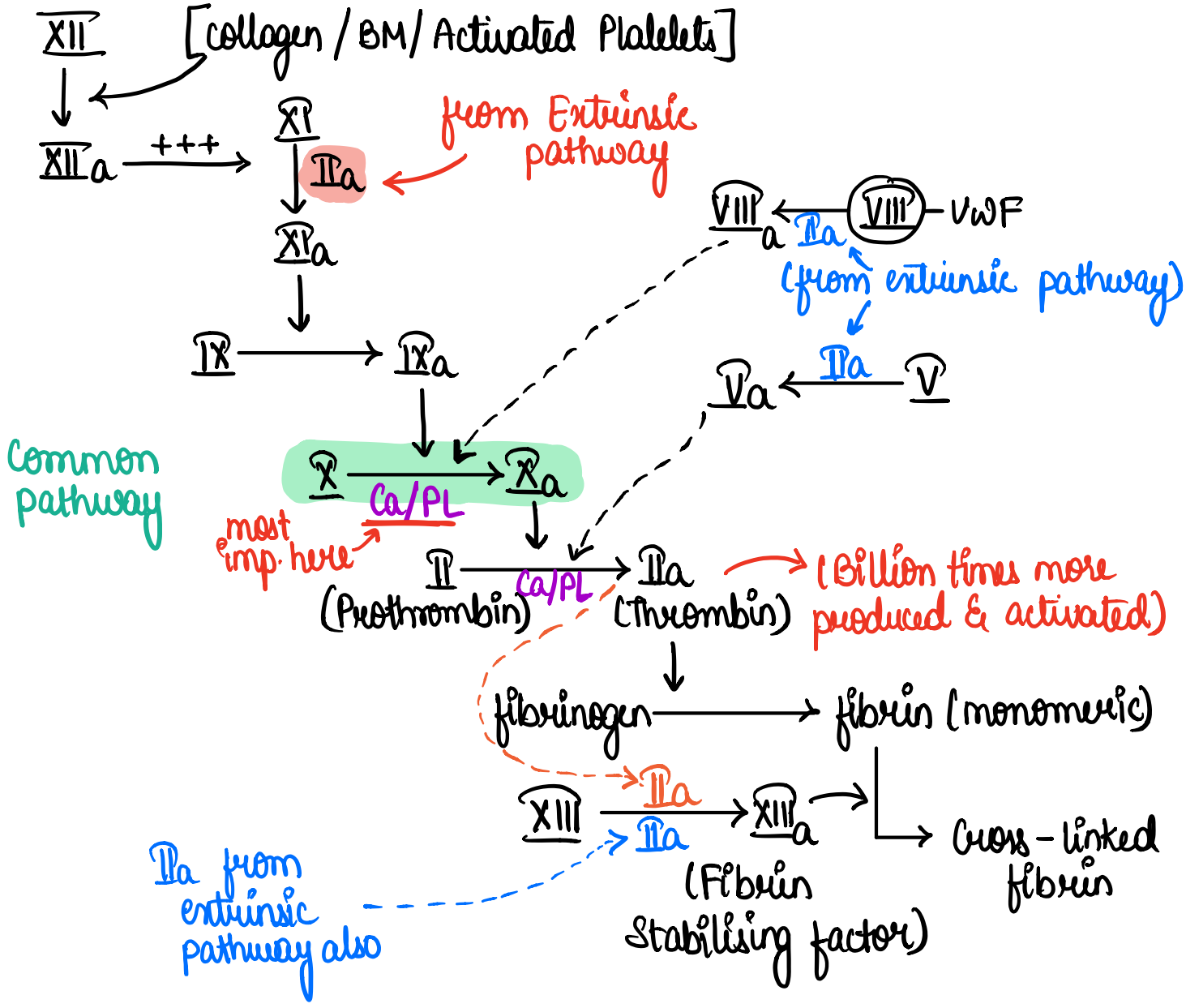


② Intrinsic Pathway:



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Factors depending on Ca/PL :

→ [Factors II, VII, IX, X] ⟹ These are also 'Vit K dependent' factors

→ II – Prothrombin
VII – Extrinsic pathway
IX – Intrinsic pathway
X – Common pathway

* For proper activation of 2,7,9,10 factors → Ca^{+2}/PL needed
* For proper production → Vit K is needed.

* **EDTA :**
Chelates Ca^{+2} in the blood sample collected & makes it unavailable for clotting factors to act on } ⟹ Blood remains in fluid state

Collecting link between Ca^{+2} & Vit K :

(uncarboxylated) CF (2/7/9/10) → (carboxylated) CF-COO^- (2/7/9/10) → attracts Ca^{+2}

(active) Vit K (Hydroxyquinone) —γ-Glutamyl carboxylase→ Vit K epoxide

Vit K epoxide —Vit K epoxide reductase, NADH → NAD^+/H^+→ Vit K (Hydroxyquinone)

Vit K antagonists (coumarin) [Epoxide analogues] eg: Warfarin ⊖ → competitive inhibitor of Epoxide reductase [replenishment of Hydroxyquinone is needed for further reactions]

Antidote for Warfarin is Vit K

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→ Prothrombin group → not dependent on thrombin
→ Factors 2/7/9/10

→ Thrombin group → dependent on Thrombin (need IIa for activation)
→ Factors 1/5/8/9/13 (I/V/VIII/IX/XIII)

Origin of CF:

→ all CF originate from Liver except F VIII originates from Endothelial cells

→ So liver failure doesn't effect F VIII.

→ Liver transplantation doesn't correct hemophilia

ANTICOAGULANTS:

ANTICOAGULANTS

- **Parenteral**
  - **Indirect**
    - ① Heparins
    - ② Fondaparinux
    - ↓ AT III ⊕ → ⊖ coagulation
  - **Direct**
    - IIa: Hirudin, Lepirudin, Bivalirudin, Argatroban
    - Xa: Danaparoid
- **Oral**
  - **Indirect**
    - ↓ Coumarin derivatives
    - ① Warfarin
    - ② Acenocoumarol
    - ↓ ⊖ Vit. K Epoxide reductase
    - Old!
  - **Direct**
    - ↓ IIa: Dabigatran (ximelagatran)
    - Xa: Apixaban, Rivaroxaban, Edoxaban
    - ↓ NOAC (novel oral anticoagulants) New!

* Thrombin-Thrombomodulin Complex ⊕ → F IIa ⊕ → Protein C + Protein S (cofactor) ⇒ ⊖ Factor V

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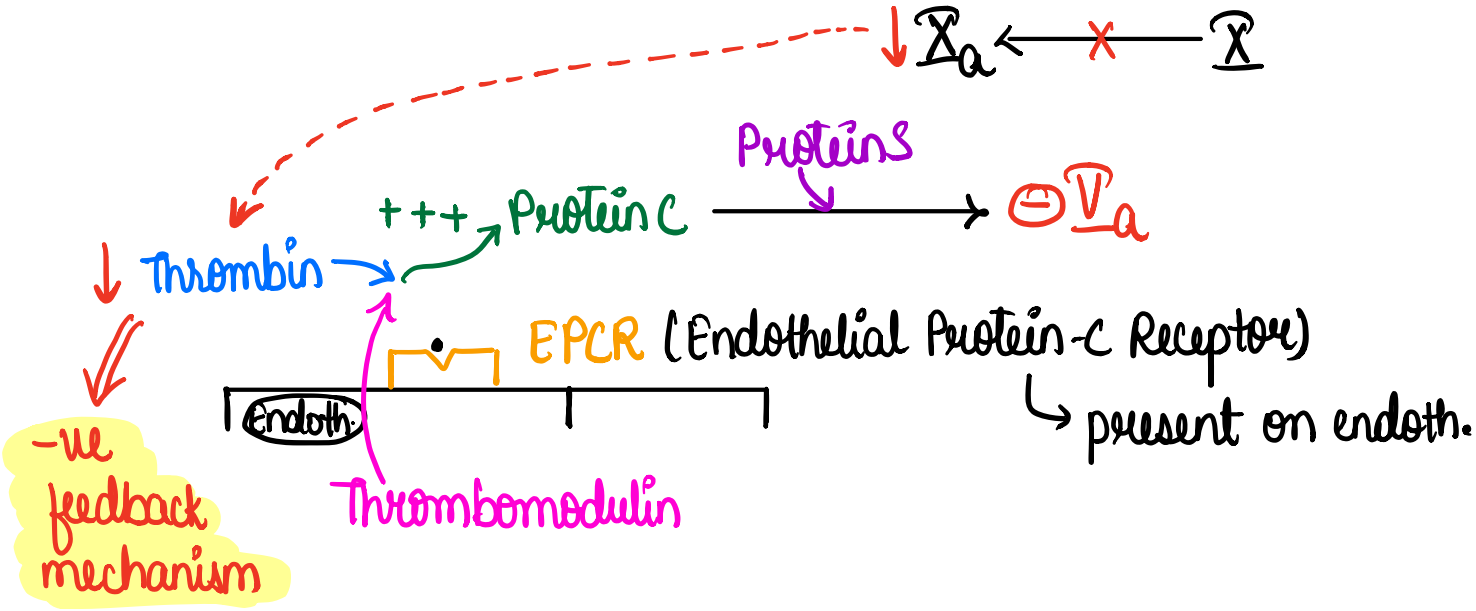
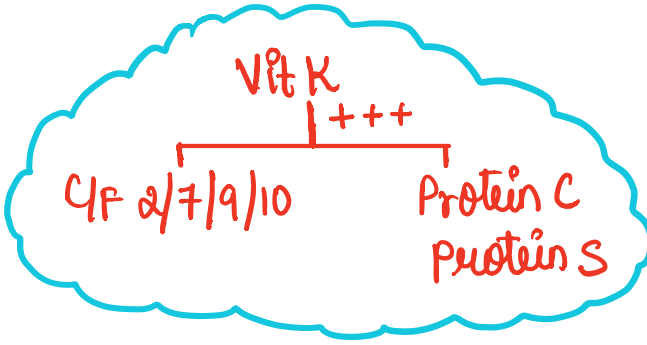


Factor V Leiden Mutation:

→ m/c inherited thrombophilia in the world

→ F V is mutated ⟹ activated Protein C resistence



INDIRECT PARENTERAL ANTICOAGULANTS:

Heparins

- Unfractionated Heparin
  - ↓
  - ⊖ IIa ⟷ Xa
  - R
  - (activated Pentasaccharide molecule c̄ long R chain)
- Low molecular wt. Heparin
  - ↓
  - Enoxaparin
  - Dalteparin
  - Tinzaparin
  - ⊖ Xa >> IIa
  - R
  - (Activated Pentasaccharide molecule c̄ short R chain)

Fondaparinux

→ ⊖ Xa only (Indirect factor Xa ⊖)

(Only Activated pentasaccharide molecule)

AT III ⊕

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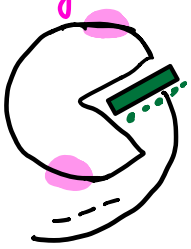
IIa (Thrombin) | Xa

* all these actions are mediated by ATIII

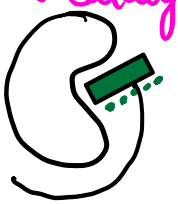
① UFH:

active catalytic sites → need R chain to activate it



IIa⊖ ✓

no catalytic sites

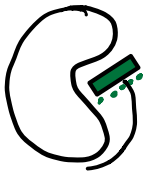


Xa⊖ ✓ ⇒ ↑ risk of HIT (Heparin induced thrombocytopenia)

② LMWH:

Shorter R chain – less inhibition of catalytic sites

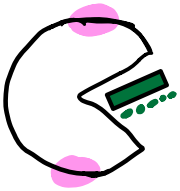
IIa⊖ ↓↓



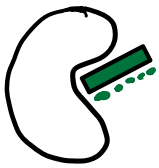
Xa⊖ ✓ ⇒ lesser risk of HIT

③ Fondaparinux:

no R chain – no inhibition of catalytic sites



IIa⊖ ✗



Xa⊖ ✓ ⇒ no risk of HIT

* Length of side chain decides the capability of heparin to ⊖IIa
* Side chains determine the Pharmacokinetics
* 'R' chain is cleared by Reticulo Endothelial System. In Fondaparinux, there is no R chain, so the clearance is mainly by the Kidney.

Monitoring Agents:

PT → External + Common pathway

aPTT → Internal + Common pathway

① UFH → aPTT – reliable

② LMWH → aPTT – not reliable

③ Fondaparinux → aPTT – not reliable

Antifactor Xa levels → common measuring agent for all 3 drugs (UFH/LMWH/Fonda)

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Effect of Protamine Sulfate:

① UFH → Protamine sulfate is very effective
② LMWH → less effective
③ Fondaparinux → not effective at all

Anticoagulant	t1/2	MOA	Metabolism	Lab. values	Overdose
① UFH	60-90min	→ AT III +++ ⊖ F IIa = F Xa	RES	→ ↑ PTT → anti F Xa activity	→ Protamine Sulfate [1mg for 100U UFH] (max - 50mg)
② LMWH (indirect parenteral)	2-7h	→ AT III +++ ⊖ F Xa >> F IIa	Kidney	→ anti F Xa activity	→ PS ≃ 60% efficacy → Enoxaparinum: 1mg PS / 1mg Enox → Dulda/Tinzaparinum: 1mg PS = 1000 mg ↑
③ Fonda	15-17h	AT III +++ ⊖ F Xa only	Kidney	Anti F Xa activity	→ no antidote → Andexanet / Ciraparantag may work
Direct ⊖: (Parenteral) ① Bivalirudin ② Argatroban	30m 45m	Direct F IIa ⊖ Direct F IIa ⊖	Kidney Liver	↑ PTT ↑ PTT	→ Dialysis (no antidote) → Dialysis
Oral Indirect: ① Warfarin	36h	Indirect (↓2/7/9/10)	Liver	↑ PT/INR (Target PT-INR - 2-3 ⇒ narrow therapeutic range & needs monitoring)	① no bleed: a) INR < 9 - skip 1-2 doses ± Oral Vit. K b) INR > 9 - skip 1-2 doses + Oral Vit K (2.5mg)

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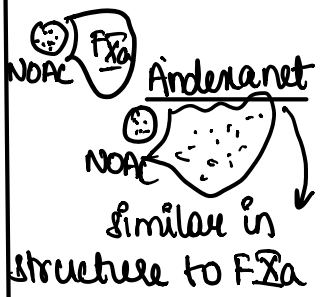
Anticoagulant	t1/2	MOA	Metabolism	Lab. values	Overdose
					② Bleeding: Stop warfarin + Vit K 10mg I.V + FFP / 4-PCC (2/7/9/10)
Oral Direct (NOAC):					
① Dabigatran	12hrs	Direct F IIa −	Kidney	↑ PTT (not used for monitoring)	Idarulizumab
② Rivaroxaban ③ Apixaban ④ Edoxaban [C/I in eGFR > 95 ml/min]	8-12h	Direct F Xa −	Kidney > liver	→ ↑ PT → anti Xa activity	Andexanet (decoy receptor) 

* Edoxaban → max. Renal clearance ⟶ so, high eGFR ↓ faster clearance ↓ ↓ action

* Kidney failure → dose of LMWH should be reduced
  → dose of UFH need not be reduced

Anti Xa activity:

Indications (LMWH) −
① Creatine clearance < 30
② Elderly (>85)
③ Body wt. (<40 kg / >140 kg)
④ Pregnancy (mechanical valves)

Target:
① Therapeutic − 0.5-1.2 IU/ml
② Prophylactic − 0.2-0.5 IU/ml

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→ In the above cases, if there is no anti FXa measurement facility @ your hospital, then prefer UFH. [Otherwise usually LMWH is used.]

Timing of test – 4h after the last dose

* Dabigatran → Idarucizumab (antidote)
  FXa ⊖ → Andexanet (antidote)
  Ciraparantag → ⊖ NOAC
  ⊖ Heparins

NOAC	WARFARIN
① Fixed dose ← Predictable → ↓ major bleed	① Unpredictable → Labile → ↑ major bleed (↓GI bleeds)
② Less complications ⇒ no monitoring	② More complications ⇒ Monitoring (INR)
③ Drug/food interaction is less	③ Drug/food interaction is more
④ Renal failure – needs dose adjustment	④ Renal failure – safe

BRIDGING:

→ b/w NOAC & Warfarin

→ A person on Oral anticoagulant } → If you want to stop oral } → Then, we can resume back to oral anticoag.

↓

it is replaced c̄ parenteral anticoagulant for some time.

⇓

Bridging (Heparin is used) [LMWH]

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① Warfarin + Heparin (Bridging) $\xrightarrow[\text{stable} > 24h]{\text{INR } 2-3}$ Stop Heparin & continue Warfarin only

② NOAC → no prophylaxis especially when used for DVT [sole anticoagulant]
↓
Bridging – Variable (Therapeutic – bridging ✓
Prophylactic – bridging ×)

Pradaxa/Dabigo ← Dabigatran, Edoxaban	→ Initial Heparin Bridge (only)	5-14d →	Sole NOAC (Dabigatran/Edoxaban)
Xarelto ← Rivaroxaban, Eliquis ← Apixaban	→ [Optional Initial Bridging c̄ Heparin]	&	Sole NOAC (Rivaroxaban/Apixaban)

Brand names (eg:)

* Edoxaban → C/I in eGFR > 95

Uses of NOAC :

① DVT /PE (prophylaxis /Rx)
② Atrial fibrillation (non-valvular)
↳ prophylaxis of stroke prevention
③ Cortico venous thrombosis

* APLA syndrome → Warfarin > NOAC

Uses of NOAC	Uses of Warfarin
① Preferred in DVT/PE (Rx/Proph.) except → APLA synd. ↓ Warfarin preferred (esp. in Triple +ve)	① Preferred in CVT & less preferred in DVT/PE → APLA synd.
② Non-valvular AF	② Valvular + non-valvular AF

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Triple '+ve' APLA: +ve for → ① Anticardiolipin ab
② Lupus ab
③ β_2 glycoprotein ab.

Drug Interactions of Warfarin:

↓ Action

① ↓ binding to albumin
- a) Sulfonamides

③ ⊖ Cyt P450:
- a) Amiodarone
- b) Diltiazem
- c) Propranolol
- d) Antibiotics:
  - ↓
  - Ciprofloxacin
  - Erythromycin
  - Fluconazole
- e) Alcohol
- f) Phenytoin
- g) Quinidine
- h) Allopurinol
- i) TCA
- j) Metronidazole
- k) Sulfonamides

④ Altered Hepatic receptors:
- a) Thyroxine
- b) Quinidine

⑤ ↓ Vit K:
- a) Antibiotics (Broad spectrum)
- b) Salicylates
- c) Cephalosporins
- d) Liver Disease
- e) ↓ absorption of Vit K
- f) Malabsorption
- g) Laxative abuse

↑ Action

① ++ Cyt P450:
- a) Barbiturates
- b) Rifampicin
- c) Ribavarin

② ↑↑ (enhanced) Clotting Factors:
- a) OCPs
- b) Pregnancy (↑ synth. of CF)
- c) Hereditary resistence to oral anticoagulants

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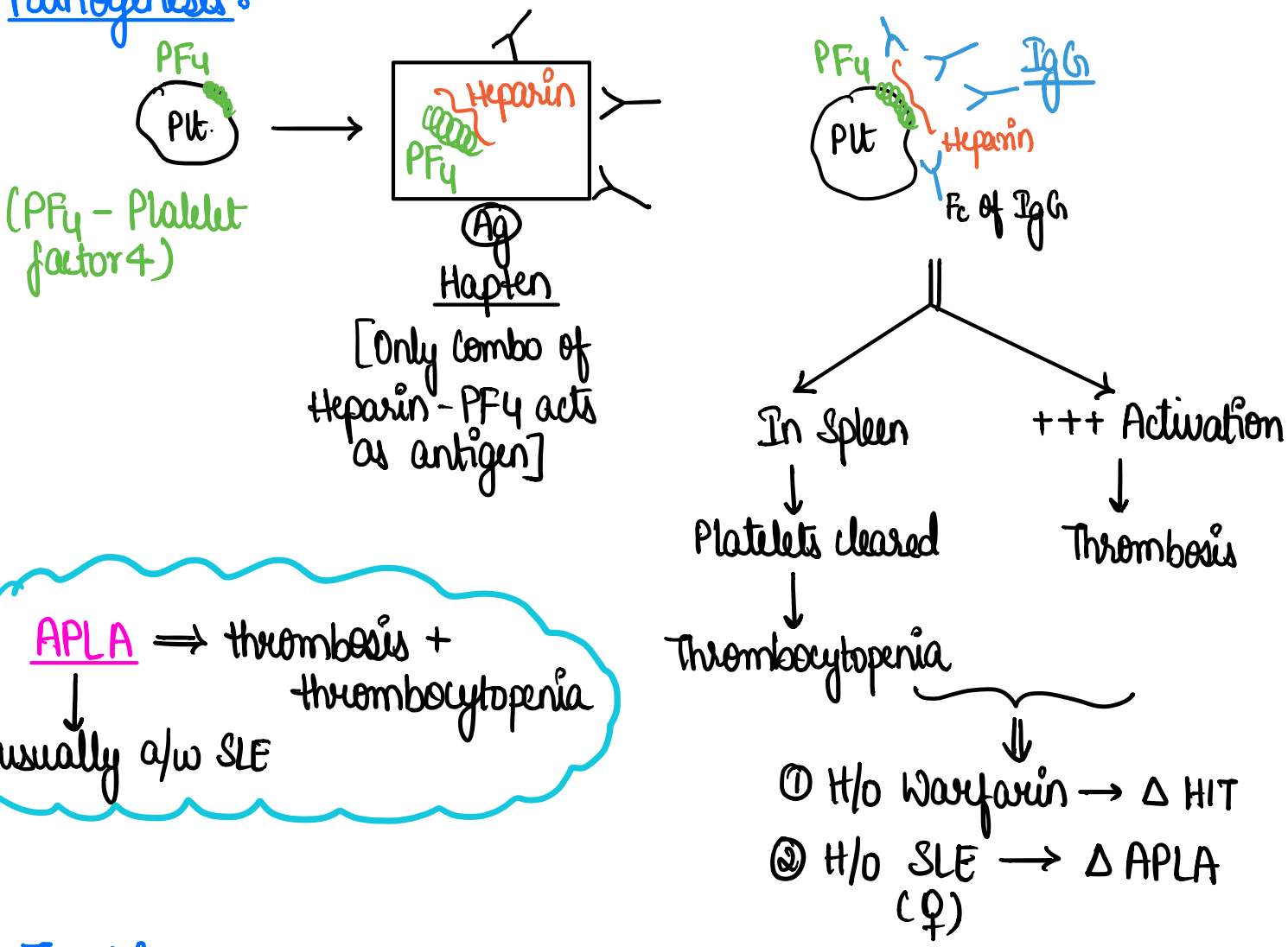
HEPARIN-INDUCED THROMBOCYTOPENIA: [HIT]

Pathogenesis:



APLA ⟹ thrombosis + thrombocytopenia
↓
usually a/w SLE

Types:

HIT 1	HIT 2
① Non-significant	① Significant
② Direct (non-immune)	② Immune (Ab mediated)
③ 10-20%	③ 1-2% [UFH - 2-3% LMWH - 0-0.8% ↓ Fonda - 0%]
④ <1-4 day of Heparin	④ >4d (D5 - D10) <4d → H/o prior Heparin use in < 3 months

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HIT 1	HIT 2
⑤ lowest point of platelet count } > 1,00,000	⑤ < 1,00,000
⑥ Thrombosis ✗	⑥ ✓
⑦ Continue Heparin	⑦ Discontinued for life time

HIT- Thrombosis Syndrome ⇒ HIT 2 + Thrombosis (HITTS)

Δ:

Clinical Δ

While on Heparin:
- Platelet < 1,00,000
  (or)
- 50% ↓ Platelets from Baseline
  (or)
- Thrombosis (venous > arterial)
  (or)
- Skin Necrosis

Pathological Δ

→ +ve HIT Ab (IgG) – ELISA (Best)

→ Alternative – functional pH aggregation assay (serotonin release)

→ ↓ Platelets (But Plt. > 1,20,000)
+ no thrombosis
+ Heparin
} – HIT 2 (can be)
→ HIT Ab to be checked for
↓
+ve

10–20% of pts on UFH/LMWH
⟷
50% of cardiac bypass

* don't Δ HIT just based on abs

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Criteria for HIT 2 :

4T →
1. Thrombocytopenia
2. Timing
3. Thrombosis
4. Other causes (obvious)

Score – [0-8]

≤ 3 – 99% (rule out HIT 2) [99% NPV – negative Predictive Value]

≥ 4 – ↑ Chance of HIT

Rx : ① Discontinue Heparin!

HELLP, HUS-TTP, HIT } don't give Platelets even in thrombocytopenia } ⇒ Thrombosis may occur

② Start anticoagulant (non-Heparin) → Irrespective of thromboses

③ Argatroban (i.v.) / Bivalirudin

↓

fix Platelets > 1,50,000

↓

(Bridge) Warfarin + Argobatran / Bivalirudin

↓ INR 2-3 (Stable > 24 h)

Warfarin only (How long?)

- Thrombosis → 3-6 mo
- no thrombosis (r/o Occult DVT) → until plt. counts recovers + 2-3 mo (DVT-ve)

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H/O HIT 2 :

↓

need anticogulant

↓

not Heparin [Acute → Fonda – 0%
Bivalirudin – 0%]

Prophylanis → NOAC
Warfarin

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Disorders of Platelet Dysfunction

	Platelet/Vascular Defects	Coagulation Defects
① Pathology	1°	2°
② Site of bleed	Superficial skin/mucus	Deep [soft tissues] (Joints / muscles)
③ Lesions :		
a) Petechiae	+++	–
b) Ecchymoses	++ (small / multiple)	++ (large / solitary & palpable)
c) Hemarthroses	–	++++
d) Deep hematomas	–	++++
④ Bleeding c̄ trauma	Minor : +++/ Persistent Post Sx : Immediate (mild)	Minor cuts – unusual Post Sx – delayed (severe)

Petechiae — Limb spanning Hematoma/ Ecchymoses — Hemarthroses

WHO CLASSIFICATION OF BLEEDING:

Grade 1 – Petechiae / Ecchymoses / Occult blood loss / spotting

Grade 2 – Gross – Epistaxis / Hematuria / Hematemesis } not responding to transfusion

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Grade 3 – Grade 2 bleeding + regular transfusion

Grade 4 – Bleeding → hemodynamic compromise
- fatal bleeding [CNS]
- Retinal bleeding

PURPURA :

→ Purplish lesions occuring d/t extravasation of RBC into dermis.

→ They are non-blanching.

PURPURA

Non-palpable [Macular]

≤3 mm – Petechiae

>3mm – Ecchymoses

Causes –

① Platelet disorders –
- a) Thrombocytopenia
- b) Platelet function defect

② Thromboemboli –
- a) DIC
- b) TTP
- c) Cholesterol/fat emboli

③ Trauma / Vascular fragility –
- a) Amyloidosis
- b) Ehler Danlos Synd.
- c) Scurvy (Perifollicular)
- d) Hereditary Hemorrhagic telangiectasia (HHT)

Palpable [Popular]

Causes –

① Vasculitis – Leukocytoclastic (HSP)
- PAN
- Rocky Mountain Spotted Fever (RMSF)

② Infectious Emboli –
- a) Meningococcus (fulminant meningococcal meningitis / Waterhouse Friedrichson Synd.)
- b) SABE (Subacute Bacterial Endocarditis)

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③ Purpura fulminans – Purpura + DIC + Hypotension } → Sepsis/DIC
(Reliform purpura) – Protein C/S def.
– APLA synd.

HHT (Hereditary Hemorrhagic Telangiectasias):

- AD → family H/o death d/t bleeding [GI/ICH]
- Telangiectasias — Skin
  Mucus memb. — [Epistaxis, GI bleed]
  Internal organs
- AV malformations → Pulm. / Hepatic / Spleen / Cerebral
- HHT is d/t 'Endoglin' protein defect.

DIAGNOSTICS:

① PT (Prothrombin time) → measured in seconds (s)

→ equates to INR [PT—INR]

→ determines Extrinsic + Common pathway

⇓

time taken to form fibrin from Thromboplastin

[Thromboplastin ⟶ fibrin]

→ Important in – ① Vit K def.
② Warfarin use
③ Liver failure

② aPTT →

→ determines intrinsic + common pathways

Phospholipids ⟶ fibrin [time taken to form fibrin from Phospholipids]

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Important in → ① Clotting factor deficiency [Hemophilia A/B]
② Acquired Clotting factor (CF) deficiency / ⊖
③ Unfractionated Heparin [for Rx monitoring]

③ TT (Thrombin time) :

- determines common pathway
  - time taken to form fibrin from Thrombin

Thrombin ⟶ fibrin

Important in – ① Fibrinogen def.
② Fibrinolytic therapy

④ Reptilase Time :

Reptilase

↑↑ Fibrinogen ⟶ (+++) fibrin

Important in – fibrinogen deficiency

⑤ Anti-Factor Ⅱa :

→ for Heparin monitoring [LMWH]

⑥ D-dimer Test :

→ for fibrinolysis eg: DVT / Pulm. embolism / DIC
→ more of a ruling out test than a confirmatory test
→ has High Negative Predictive Value (NPV)
→ has high sensitivity.

⑦ ThromboElectro Graph : for Hyperfibrinolysis

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⑧ Platelet function analysis (PFA - 100)
Platelet Aggregometry
Flow cytometry
} ⇒ Platet function assessment

PLATELET DISORDERS :

① Thrombocytopenia :

Platelets < 1,50,000/mm²

Risks – ① 50,000 - 1,00,000 → major trauma
② 20,000 - 50,000 ⇒ minor trauma (Avoid Surgeries)
③ < 20,000 ⇒ Spontaneous bleeding

* ITP → less risk of bleeding even if Plt. count < 2,000 because, it is a purely a quantitative defect & there is no qualitative defect.

④ < 10,000 ⇒ Severe bleeding

Etiology :

Thrombocytopenia

↓ production

① Hypocellular marrow
a) Aplastic anemia
b) Hypocellular MDS
c) Drugs [Thiazides/Anti-biotics/Chemotherapy]
d) Alcohol
e) Cirrhosis → Hypersplenism
↓
Hypercellular BM

↑ Destruction

① $\boxed{1^\circ}$ → Idiopathic
a) ITP
b) Evans Syndrome (ITP + AIHA)

② $\boxed{2^\circ}$ →
a) Infections [HIV/HCV/HSV/CMV/H. Pylori]
b) CTD – [SLE/APLA]

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↓ production

② Hypercellular marrow:
- a) Myelofibrosis
- b) Hematological/solid organ tumors (metastasis)
- c) Granulomas
- d) Leukemias
- e) Megaloblastic anemia

Thrombotic microangiopathies

MAHA

↓ Platelets — End-organ dysfunction

→ MAHA – Schistocytes (P.S)
↑↑ LDH (i.v. hemolysis)

→ End-organ dysfunction –
- a) Renal
- b) CNS
- c) GIT

↑ Destruction

c) Drugs – Heparin Induced Thrombocytopenia
- Abciximab/ Quinidine
- Sulfonamides / Vancomycin (Immune-mediated)

d) Allo-immune – Post Transfusion purpura (rare)

e) Non-immune –

(i) Thrombotic microangiopathies:
- HUS-TTP
- DIC
- HELLP /Preeclampsia
- Drugs (Clopidogrel / Ticlopidine)

(ii) Abn vascular syndromes:
- Cardiopulmonary bypass
- Continuous Veno venous hemodialysis (CVVH)
- IABP
- Cavernous Hemangioma
- Prosthetic valves

(iii) Viral infection:
- Dengue

Thrombocytopenias

Clumps → (likely) Pseudothrombocytopenia [d/t EDTA] → Repeat c̄ Heparin/ Citrate

no clumps → True Thrombocytopenia → CBC / Smear

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CBC / Smear

- Isolated ↓ Platelets + (N) smear → Culprits?
  - Yes → 2° ATP
    - Drug-induced
    - Infections
  - No → 1° ATP
- ab(n) CBC / smear →
  - Spherocytes → Evans / Hypersplenism (AIHA+)
  - Schistocytes → Thrombotic Microangiopathy (TMA)
  - Pancytopenia / blasts → MDS / leukemia
    - → Leukoerythroblastic reaction (seen in Myelofibrosis)

Sequestration of Platelets:

1. Spleen – Hypersplenism (Splenomegaly)
2. Cirrhosis

Ab(n) distribution of Platelets:

1. Dilutional → Post op
   → Massive trauma
2. Hypothermia
3. Unknown
   - Babesiosis
   - RMSF
   - Gestational thrombocytopenia
     - usually Plt count is 70K
     - Usually a safe condition
     - no Rx needed
     - rule out other dis. like APLA.
   - Ehrlichiosis

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ITP :

- Idiopathic thrombocytopenic Purpura

ITP
- Acute ITP
- Chronic ITP
  - 1°
  - 2°

→ ♀
→ 15-50yrs
→ Δ of exclusion

Pathogenesis :

① 1° Chronic ITP : [Type 2 HSR]

Auto abs
- Platelets
  ⇓
  Peripheral destruction
  ↓
  in Spleen by Splenic macrophages
  - (m/c) GPIIb/IIIa
  - GPIb
- Megakaryocytes (less)
  ↓
  ↓ production of Platelets

⇓
Splenic tyrosine Kinase needed for Splenic destruction

C/f : [♀ > ♂]

→ Insidious onset ⇒ Mucocutaneous bleeding [gum bleeding / menorrhagia]

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→ Hepatosplenomegaly, Lymphadenopathy } → Common in 2° ITP
Not seen in 1° ATP

Δ: ① CBC – isolated thrombocytopenia [<1,00,000 but may reach <20,000]

Life span of Platelets:
(N) – 10 days
ITP – hours

② PS – (N) ± Giant Platelets (non-specific)
↓
rule out other causes of 2° ITP

③ BM Biopsy – Cellular Marrow
↑ Megakaryocytes production as a response

(not definitely needed inv. in ITP)

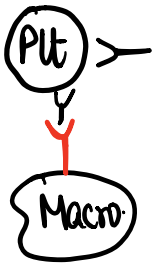
If CBS/PS is ab(n) ⟶ then we do BM Biopsy

* Hb testing is not useful & non-specific

Rx: Indications – <30,000 (or) bleeding / Trauma / Surgery

1st line –

① Steroids → Chronic / maintenanance
- Prednisolone / Dexa ⟹ 1-2 wks
- not given in acute conditions [steroids usually take 1-2 wks to come into action.

→ 

Splenic macrophages have FcR that recognize platelets coated C̄ Abs.

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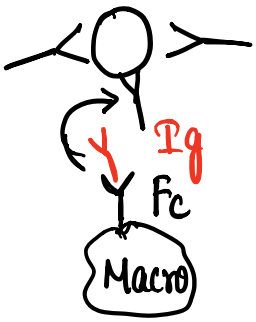
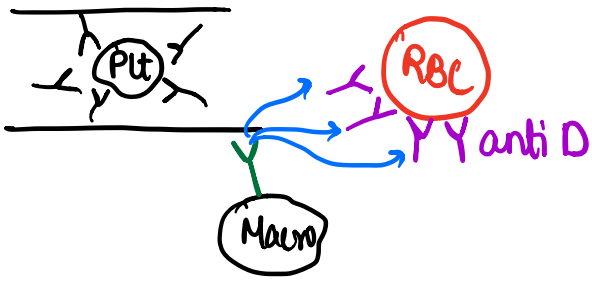
→ Steroids downregulate the FCR of splenic macrophages
→ ↓ production of anti-Platelet abs
→ 10-80% initial response
20% sustained remission



② <u>I.V. Ig</u> → Acute / Rapid
→ 1 dose action lasts for 2-6 wks
→ 80% initial response
→ no sustained remission
→ 1g/kg - dose used
→ immediate action occurs
→ IV Ig saturates FcR c̄ the Ig of I.V. Ig

③ <u>Anti-D</u> [anti Rh D]:
→ not to be used in severe anemia → it worsens anemia
→ not preferred



② <u>2nd line</u>: [maintenance]
① Romiplastin / Eltrombopag [TPOr agonists]
② Rituximab (anti CD 20) - anti B cell Mab
③ Splenectomy (65% cure) → not preferred
④ Azathioprine / Cyclophosphamide / Mycophenolate mofetil
⑤ Danazol (↓ Plt. clearance)

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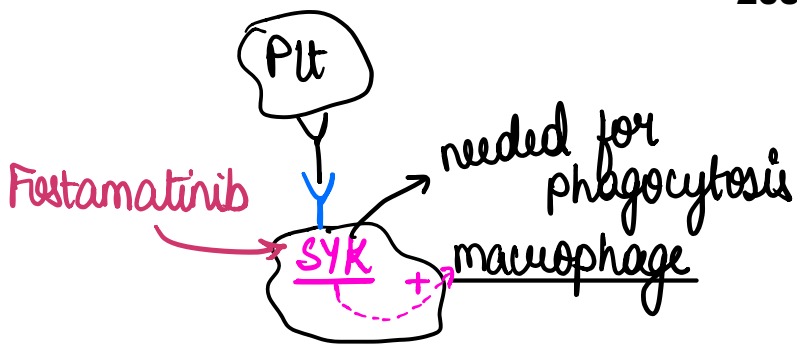
① Chronic / refractory cases :

① Fostamatinib –

→ ⊖ Splenic tyrosine Kinase

→ ⊖ Phagocytosis

→ oral – 75-150 mg BD



② Bleeding :

① EACA / Tranexamic acid
↓
Epsilon Amino Caproic acid

② IV Ig

③ Platelet transfusion

PLATELET FUNCTION DISORDERS :

	Inherited	Acquired
Adhesion	① Bernard Soulier Synd. ② VWD	① Uremia ② Acquired VWD
Aggregation	① Afibrinogenemia ② Glanzman thrombasthenia	① Aspirin / P_2Y_{12}⊖ / GP II b III a ⊖ ② Multiple myeloma
Granule release	① Chediak Higashi synd. ② Hemansky Pudlak ③ Gray Platelet synd. ④ Storage disorders	① Aspirin ② Liver disease ③ MPN (d/t abn Plt. products) ④ Cardio Pulmonary Bypass

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PLATELET AGGREGATION TESTS :

① **Bleeding Time** → Ⓝ - 3-8 mins [lot of false '+ves'] – not preferred

② **PFA-100** →

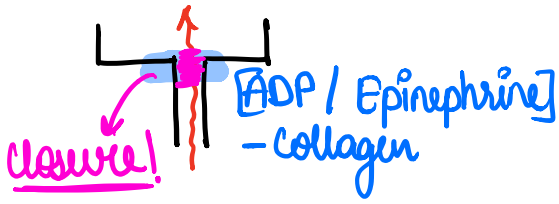
Platelets aggregate on exposure to [ADP/ Epinephrine]-collagen

⇓

On aggregation, they close the aperture

⇓

The time taken for closure is calculated



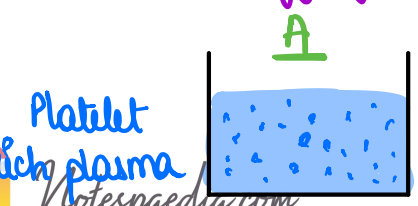
Ⓝ closure

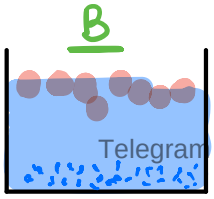
- 75-130s (C̄ collagen-ADP)
- 100-180s (C̄ collagen-Epinephrine)

↑ Closure time

- Coll/ADP + Coll/Epi → most Plt. disorders
- Coll/Epi only → Storage pool disease
- Coll/Epi >> Coll/ADP → Aspirin

③ **Platelet aggregometry :**





Arachidonic acid
Epinephrine
Collagen
ADP
Ristocetin

} Added aggregates

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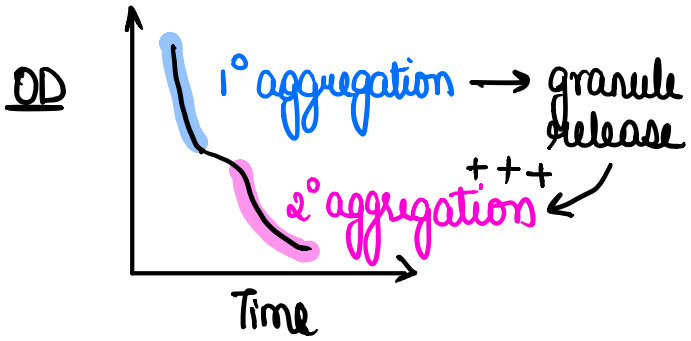
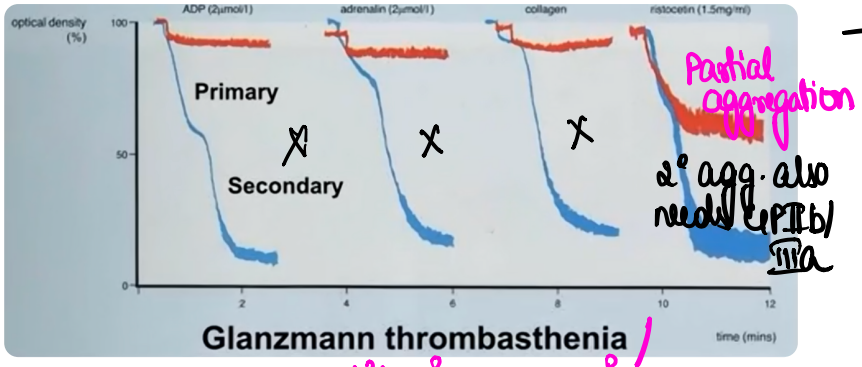
A	B
↑ Optical Density (OD)	↓ Optical Density (OD)
↑ light absorbence	↑ Light absorbance
↓ light transmission	↓ Light transmission



Arachidonic acid → COX → GpIIb/IIIa → fibrinogen

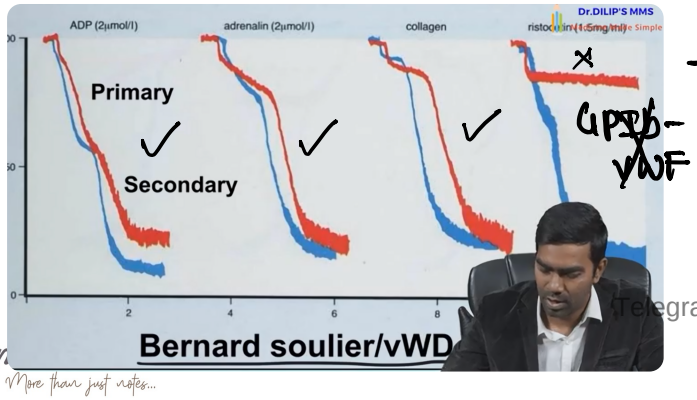
Collagen → Phospholipase C → GpIIb/IIIa

Ristocetin → GpIb → ↑ VWF interaction

① 

→ no ↓ OD because there is no aggregation d/t defective GpIIb/IIIa (or) fibrinogen

→ Aggregation ĉ
① Absent – ADP/collagen/Epi
② Partial – Ristocetin

② 

→ Absent Ristocetin aggregation d/t defective GpIb/VWF

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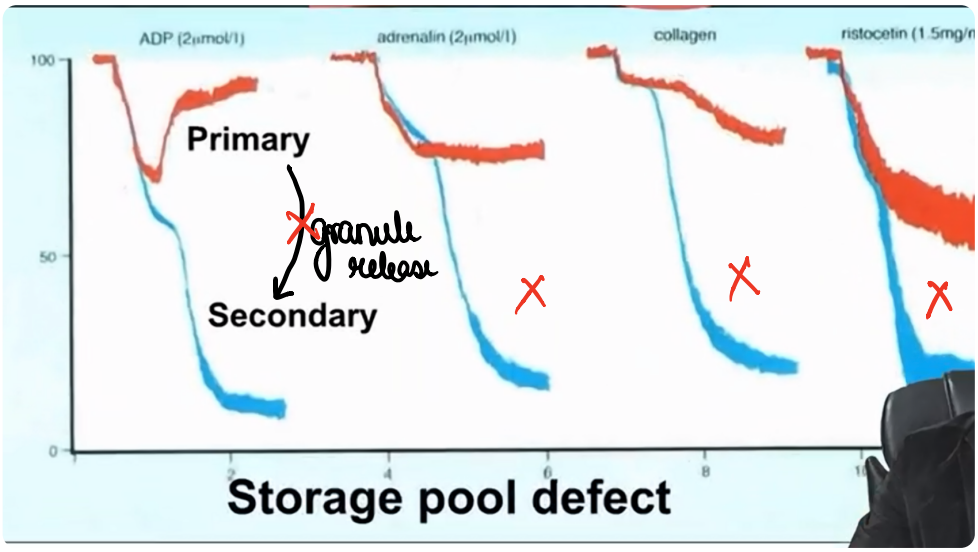
③



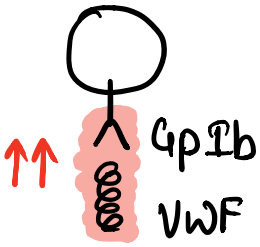
④ Aspirin – ↓ aggregation c̄ AA

– m/c cause of Platelet dysfunction dis.

– m/c cause defective Platelet function in the world.

⑤ Clopidogrel – ↓ aggregation c̄ ADP

⑥ VWD (Pseudo) – [2B]



⇒ ↓ free VWF
Platelets ↓
↑ aggregation c̄ Restocetin

⑦ Uraemia –

↓ aggregation
↓ adhesion

Rx –
① DDAVP (Desmopressin)
② Cryoprecipitate
③ Correct anemia
④ Stop anti platelet agents
⑤ Hemodialysis

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Disorders of Coagulation

CLASSIFICATION :

Coagulation Disorders

- **Congenital**
  - 80% → Hemophilia A → F VIII deficiency
  - 20% → Hemophilia B → F IX deficiency (Christmas disease)
  - Others – F XI def. [Hemophilia C]
    F XII def.
    F XIII def.
- **Acquired** (m/c)
  - Causes –
    1. DIC
    2. Liver Disease (m/c)
    3. Vit K deficiency
- **X-linked Recessive**
  - ♀ – carriers
  - ♂ – Severe

⇒ F VIII mutations
- 50% → Mutations → Missense, Frameshift, Deletion
- 50% → Flip Tip Inversion (Poor quality Proteins produced)

CLINICAL FEATURES :

2/3rd cases ⇒ family History

1/3rd cases ⇒ no family history

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Class	Clinical Severity	Factor Levels	Prophylaxis / Rx
① Physiological	–	≥ 50%	–
② Mild	Severe trauma	5 – 50%	Individualised [DDAVP] ↓ Desmopressin → ↑ release of vWF from WP bodies of endoth. [vWF carries FVIII with it]
③ Moderate	Mild trauma	1 – 5%	
④ Severe	Spontaneous bleeding	<1%	Continuous / Regular Rx

C/f of Severe Coagulation Disorders :

① Deep [Hematomas] → Soft tissues (muscle)
Joints [Hemarthroses]

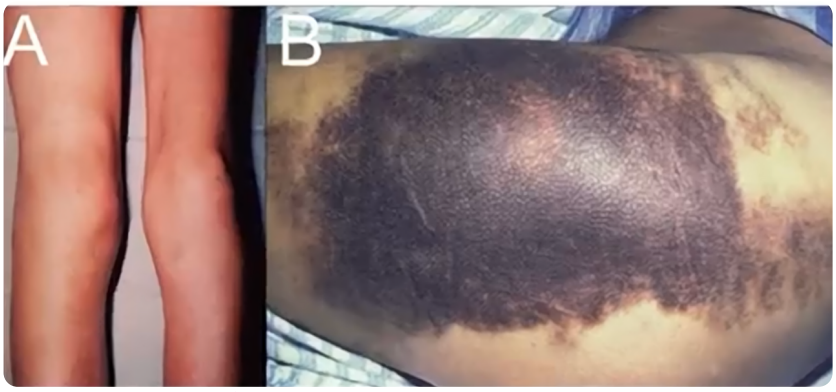
② Echymoses → Solitary / Large & palpable

③ Trauma / Surgery ⇒ delayed bleeding

④ Mucosal bleeding / Intracerebral Hemorrhage [rare]
(Genitourinary / GI bleeding)

⇒ If Chronic / Recurrent :
⇓
Hemophilic Pseudotumor
[Cystic, encapsulated lesion]

→ If Bone :
± Osteolysis
± Reactive new bone formation



Hemarthrosis Ecchymoses

Hemophilic Pseudotumor
cystic lesion → mixed ⊂ areas of blood

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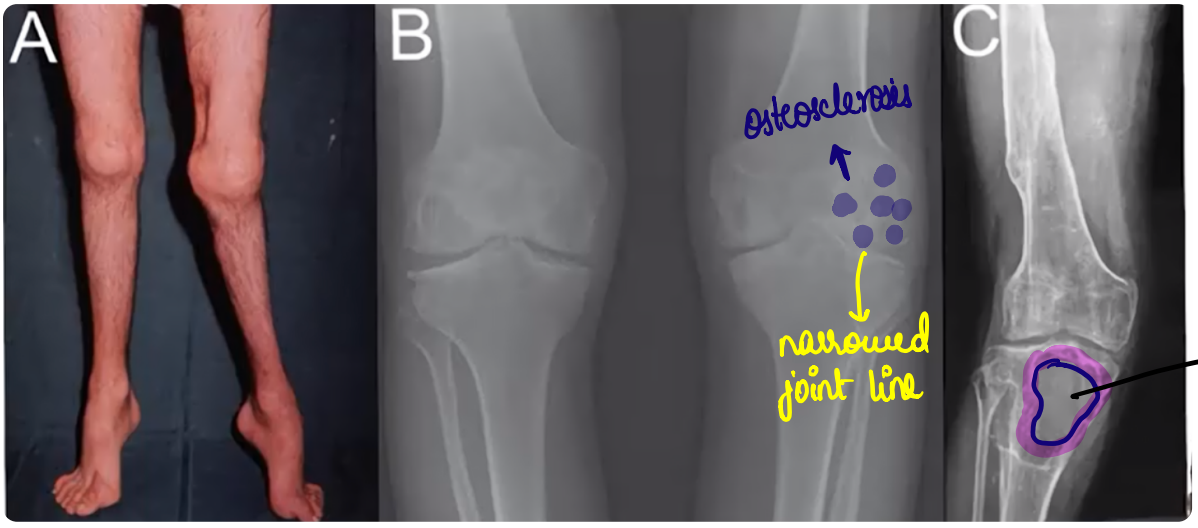

Hemarthrosis (Chronic → destroyed joint)

Hemophilic Pseudotumor

PROPHYLAXIS :

Types → ① Episodic – (on demand) ⇒ @ time of bleeding

② Intermittent – (periodic) ⇒ @ time of high risk of bleeding (eg: Sx)

③ Continuous – (regular) ⇒

1° – < 3yrs (or) before 2nd large joint bleed

2° – ≥2 large joints bleeds but before arthropathy

3° – after arthropathy

DIAGNOSIS :

Clinical features (eg: Hemophilia/ disorder of Intrinsic pathway) —suggesting of clotting factor disorders→ aPTT / PT / INR

↑↑↑ (Intrinsic + common pathway) — N N (Extrinsic + common pathway)

D/D – ① CF deficiency

② CF inhibitors (abs formed) — m/c against F VIII

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D/D

↓

50 : 50 mix / study

Pt. plasma — Control plasma

↓

aPTT — corrected → CF deficiency; not corrected → CF inhibitor

rule out VWD
⇓
VWF : Ag = (N)
VWF : F VIII binding } = (N)

rule out Platelet disorder
⇓
PFA - 100 = (N)

Confirmation
⇓
If F VIII / IX levels / activity ↓↓

TREATMENT :

Prophylaxis (Continuous / regular)

[maintain F levels atleast 1-2% to prevent spontaneous bleeding]

Indications – ① Severe disease (<1%)

⇓

Factor concentrates

↓

Dose

Malmo protocol → 25-40 U/kg

Utrecht protocol → 15-30 U/kg.

F VIII def. → 3 times a week

F IX def. (↑ t½) → 2 times a week

Ideal time to start } ⇒ <3 yrs (ideal : 1-1.5 yrs)
[85% of year ! ⇒ 45/52 wks]

Bleeding

① Life threatening – ① Head injury
② ICH
③ Major Sx

Target – 80-100%

Duration – maintained for 10-14d

Dose – F VIII – 50U/kg
F IX – 100U/kg

② Minor Sx / Other bleeds (Joints) –

Target – 50%

Duration – maintained for 3-5d

Dose – F VIII – 25 U/kg
F IX – 50U/kg

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Products used in case of Bleeding :

Factor VIII

① **Intermediate purity** –

a) Humate P → not used now d/t high transmission rate of HIV, HCV, etc.

② **Recombinant F VIII** –

1st – Recombinate (has albumin)

2nd – Helixate

3rd – Advate (no albumin)

③ **Combination of F VIII c̄ Fc of Ab :**

Eloctate (F VIII – Fc)

Factor IX

↓

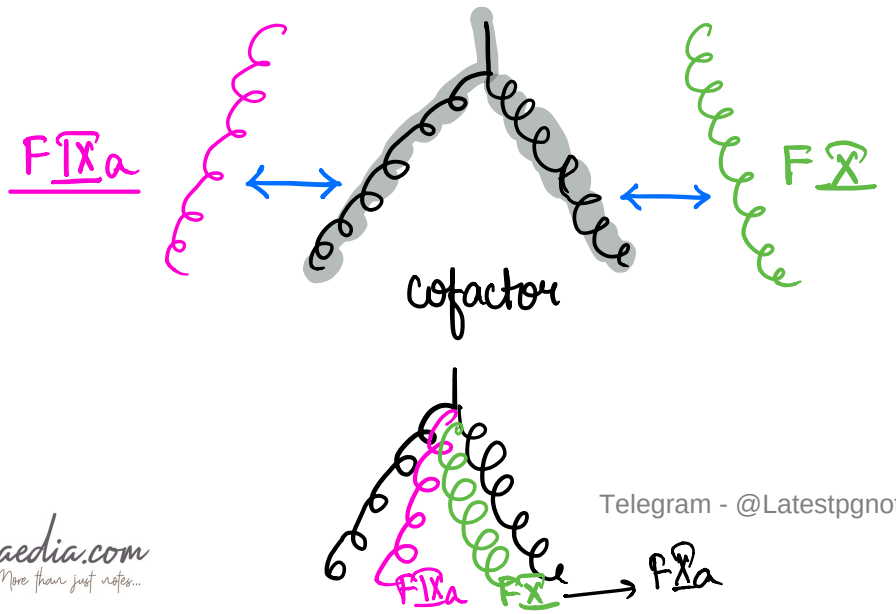
① Rixubis

② Alprolix

Others : ① DDAVP (mild)

② EACA
③ Cryoprecipitate } can be used as an adjunct

④ Emicizumab → Bi-specific Ab



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ACQUIRED F VIII INHIBITORS :

→ 30% severe hemophiliacs can acquire this

→ When we give F VIII to the Hemophiliac pt., the body may consider it as a foreign body & abs may be produced against it.

→ also considered as 'Factor VIII ineffective'

→ occurs in people c̄ <50 days exposure

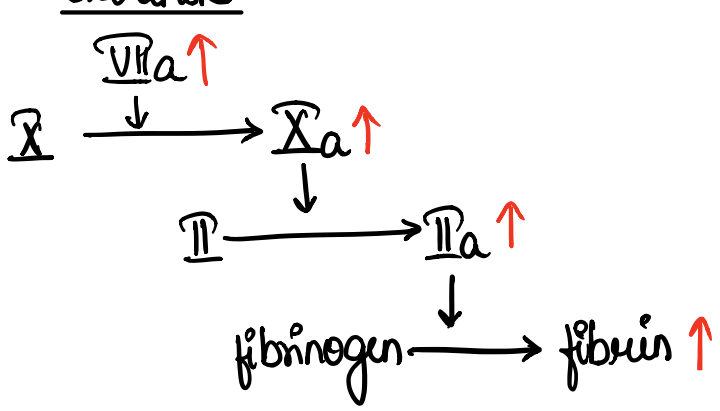
People @ risk → Post partum ♀ (multigravida)
Autoimmune disorders
Lymphoproliferative disorders

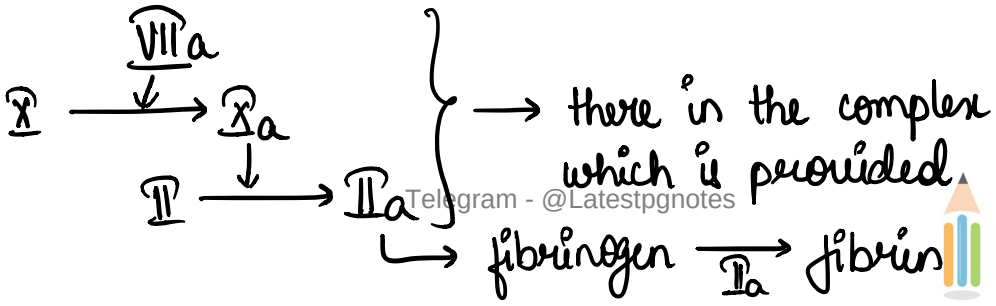
Δ → aPTT ↑
↳ & uncorrected c̄ 50:50 mix / study
[done using Bethesda titres]

Rx → ① F VIIa concentrates (has less t½)
↳ so multiple infusions needed

② High dose F VIII

③ FEIBA (Factor Eight Inhibitor Bypassing agent)
→ 4 complex PCC (has activated 2, 7, 9, 10 factors)





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④ Emicizumab

⑤ Immunosuppressants → ① Steroids
② Cyclophosphamide
③ Rituximab

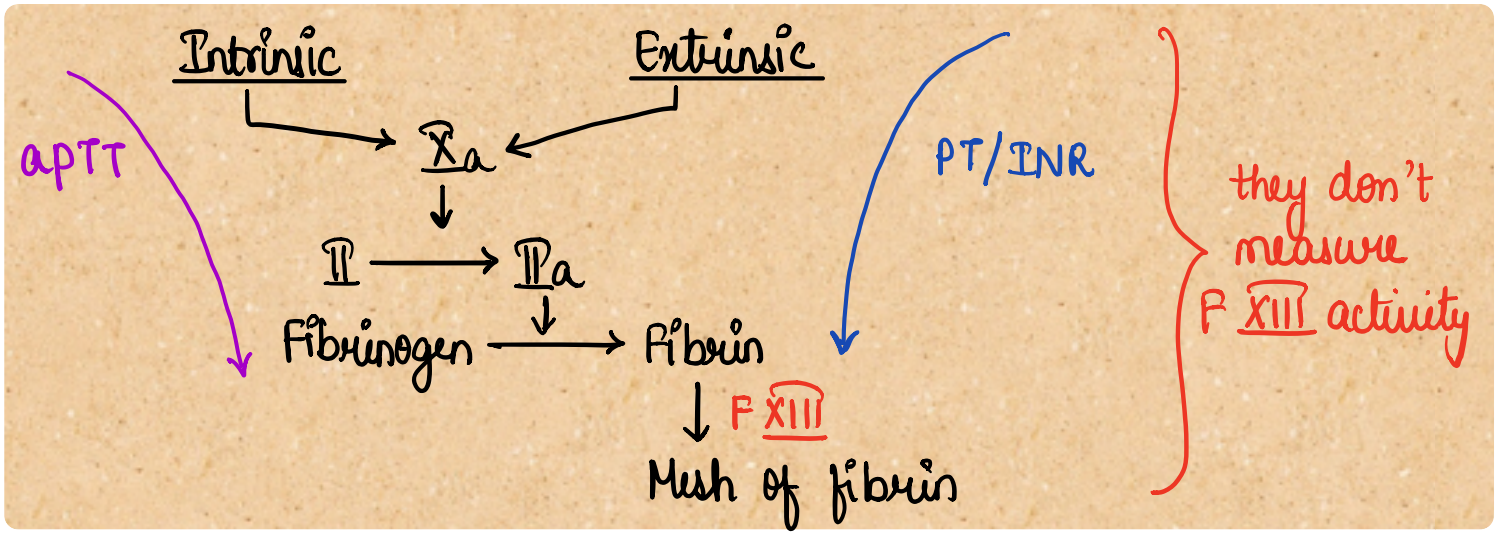
↕ I.V. Ig (or) Therapeutic Plasma Exchange

FACTOR XII DEFICIENCY :

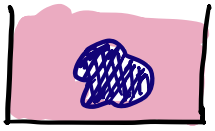
→ ↑ aPTT + corrects c̄ mixing
→ PFA-100 Ⓝ / Platelets - Ⓝ / PT/INR - Ⓝ
→ No bleeding

FACTOR XIII DEFICIENCY :

→ Delayed Umbilical cord / stump bleeding
→ aPTT - Ⓝ / PT/INR - Ⓝ / PFA-100 - Ⓝ



→ Δ - Urea Clot Lysis Time



5 M (molar) urea solution is used here, which lyses the clot & the time taken to lyse the clot is calculated.

Ⓝ time = > 24 hrs
If time taken is < 24 hrs ⇒ clot unstable ⇒ F XIII deficiency

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FACTOR XI DEFICIENCY:

→ Hemophilia 'C'
→ Slow oozing from mucus membrane [GU/ENT] — following a minor Sx
→ ↑ aPTT

Rx - FFP (Fresh Frozen Plasma)

DIC (Disseminated Intravascular Coagulation):

→ An acquired condition
→ It is a form of Thrombotic Microangiopathy (TMA)

Triad:

MAHA → Schistocytes (in P.S) / i.v. hemolysis
⇓
↑ LDH
↓ Sr. Haptoglobin

↓ Platelets

End organ failure
↓
① Kidney
② CNS
③ GIT

D/D → ① HUS-TTP

↑↑ (DIC) ← D-dimer, PT/INR/aPTT { HUS-TTP, DIC } D-dimer, PT/INR/aPTT → (N) [HUS-TTP]

Etiology →
① Sepsis (grm -ve sepsis) (m/c)
② Other infections (Cl. Welchii/ Semue falciparum)
(viral - HIV/ CMV/ Varicella)
③ Malignancy (AML - M3) - Acute Promyelocytic leukemia
(GI Adenocarcinoma)
④ Obstetric causes (Septic abortions/amniotic fluid embolism)

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⑤ Trauma / Severe SIRS
⑥ Mismatched transfusions
⑦ Hypothermia / Heat stroke
⑧ Snake Venom

Pathophysiology –

++ Coagulation Pathway
- → (↓Platelets) Platelets consumed
- → MAHA (Schistocytes)
- → Clotting factor consumption
  - → ↑PT/INR, ↑aPTT
  - → Bleeding
- → Thrombosis (microvascular) → End organ dysfunction/failure
- → ++ fibrinolytic pathway → ↑D-dimer, ↑FDP

⇓ Consumptive Coagulopathy

macrovascular thrombosis + bleeding ⇓ HIT

Chronic DIC → ↑↑ CF synthesis
↑↑ Platelets

Δ – By clinical history (underlying cause can also be known)
Acute → D-dimer ↑ / ↓Platelets / PT, aPTT, INR ↑
Chronic → D-dimer ↑ (Platelets & PT/aPTT/INR variable)
→ Schistocytes in P.S

Rx – ① Treat the underlying cause
② Platelets / FFP → Target fibrinogen > 100 mg/dl

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VITAMIN 'K' DEFICIENCY :

Etiology →
1. Malnutrition
2. ↓ absorption of Vit K (Antibiotics / Malabsorption)
3. Liver disease
4. Warfarin
5. Hemorrhagic disease of newborn (generally bleeds on Day 2-4)

Δ - PT/INR ↑, aPTT ↑ | Platelets, D-dimer, PFA-100 } (N)

Case discussion – A 45 yr old, ♂ pt. c̄ H/o Sepsis (urosepsis) 15 days back was diagnosed c̄ DIC. There is evidence of Schistocytes in P.S / ↑ D-dimer / ↑ PT-INR / ↓ Platelets c̄ Renal failure.

⇓

Pt. was started on Meropenem

⇓

Pt. was then stable except for there were still schistocytes in P.S & ↑ PT-INR (LFT – (N)) [Meropenem – Day 12]

⇓

℞ - Stop Meropenem
→ Inj. Vit K 1 mg × 2 days

[Meropenem should be stopped usually on 8th day if the Pt. becomes stable → Otherwise, it ↓ the gut flora & Vit K absorption ↓]

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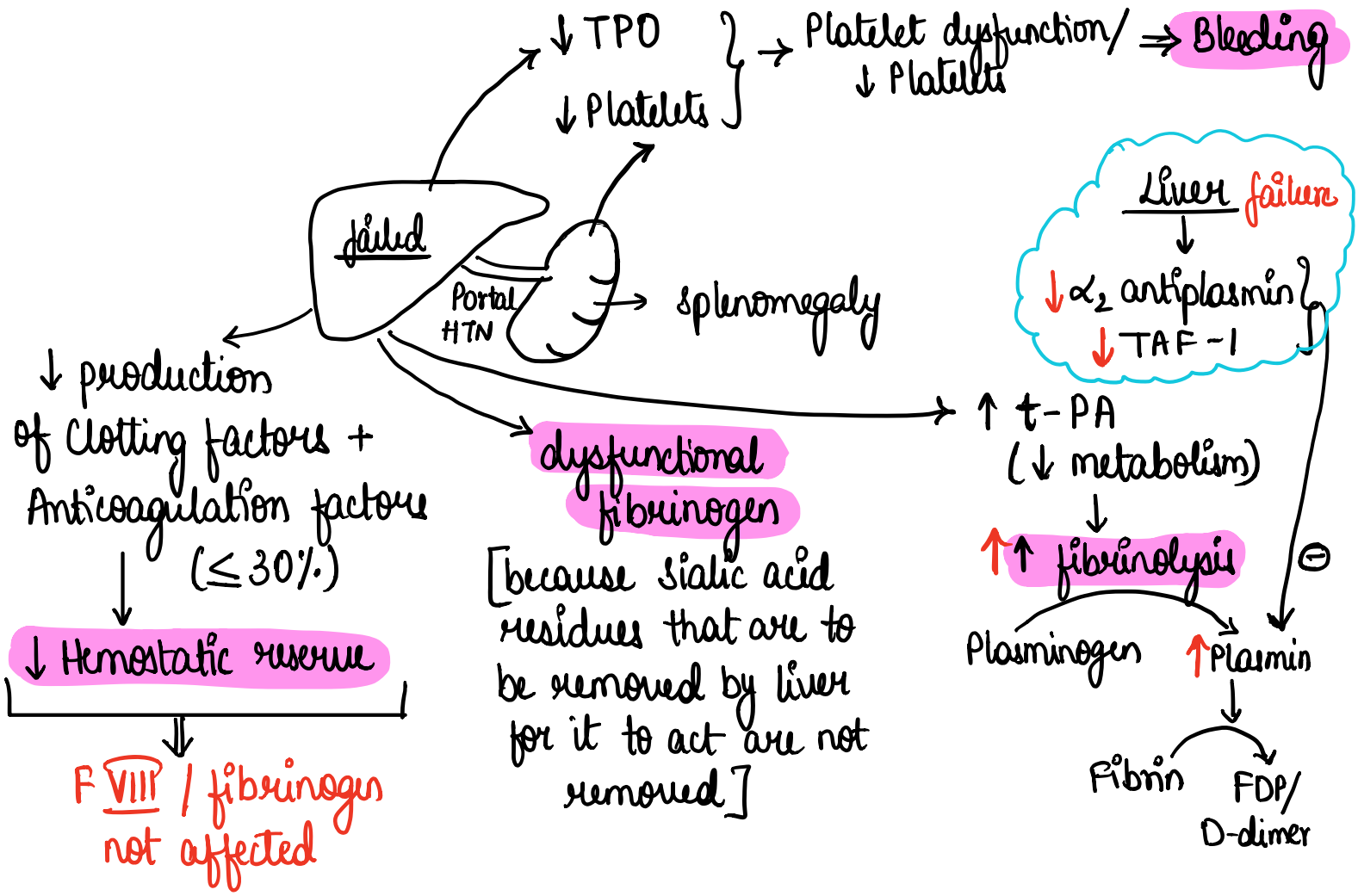
Rx :

	Prophylaxis (to prevent Bleeding)	Treatment (to cure bleeding)
Adults →	Ind. – Prior to Liver Biopsy [5mg/day – PO (or) 10ml slow I.V]	10mg slow I.V. Repeat × 2 days [if severe, → 4 complex PCC given]
Newborns →	All are given 1mg I.M.	1mg IM 6hrly.

LIVER DISEASE :



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	PT	aPTT	TT	Fibrinogen	D-dimer	BT	Platelets
① Vit K def./ Warfarin	↑↑↑ (normalises c̄ Vit K)	↑	N	N	N	N	N
② Aspirin	N	N	N	N	N	↑	N
③ Liver failure							
Early	↑↑↑	N	N	N	N	N	N
Late	↑↑↑	↑	N/↑	N/↑	N/↑	↑	↓
④ Uremia	N	N	N	N	N	↑	N
⑤ DIC	↑↑↑	↑↑↑	↑↑↑	↓↓	↑↑	↑↑	↓↓
⑥ TTP	N	N	N	N	N	↑↑	↓↓
⑦ Heparin (UFH)	↑ (mild)	↑↑↑	↑↑	N	N	N	N

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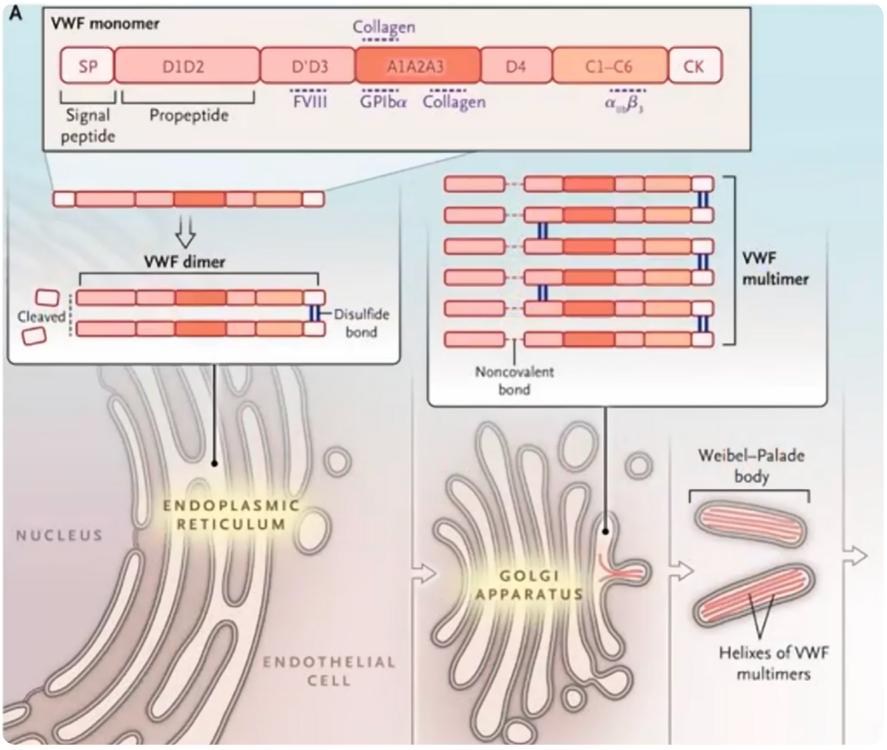
Von Willebrand Disease

→ Von Willebrand Disease (VWD) → is a bleeding disorder

→ m/c inherited bleeding disorder

SYNTHESIS OF VWF:

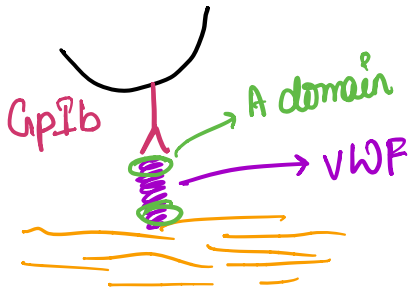


VWF Monomer
(synthesised by Endothelial cells)
↓
VWF Dimer
↓
VWF Multimers
↓
Storage
(Weibel-Palade Bodies)
↓
Release

① VWF Monomer:

→ synthesised by endothelial cells

Domains – ① $A_1A_2A_3$ (A domain) → binds to GPIα & Collagen



→ In the form of multimers, A domain @ one end binds to Gp Ia & A domain @ the other end binds to Collagen

② D_1D_3 (D domain) → binds to Factor (F) VIII

– so, t½ of F VIII ↑ & prevents its degradation.

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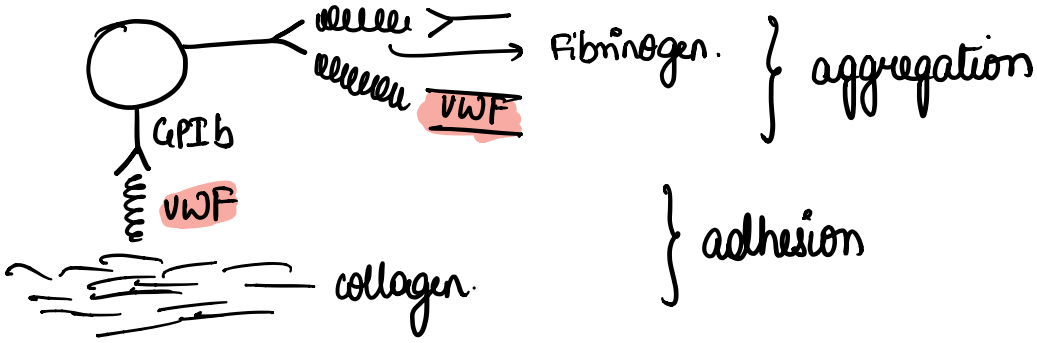
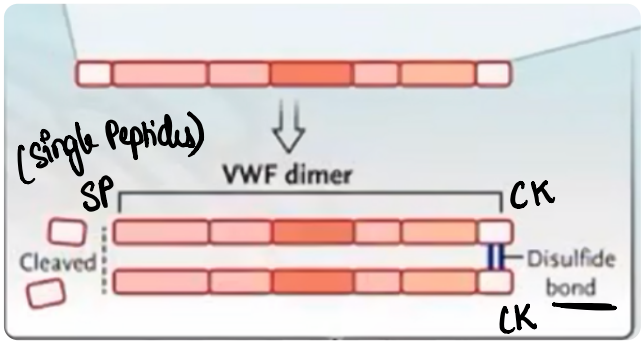
③ C domain (C_1–C_6) → binds to $\alpha_{IIb}\beta_3$ [GpIIb/IIIa]



② VWF dimer:



→ Single Peptide molecules are cleaved

→ CK molecules of both monomers are joined by disulphide bonds.

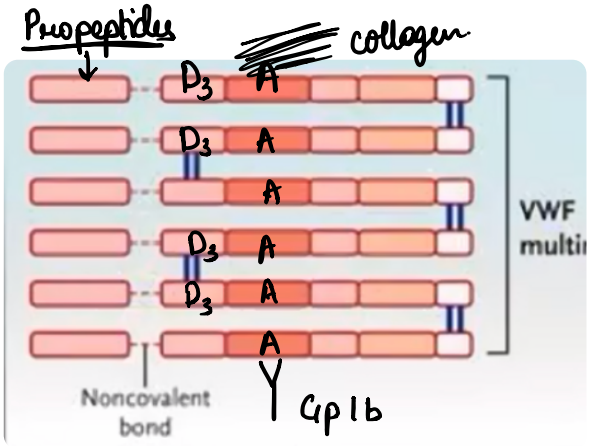
→ Dimerisation occurs in → Endoplasmic Reticulum

③ VWF Multimer:

→ Each dimer is linked to another dimer by disulphide bond (disulphide bridges) @ D_3 domain

→ Pro-peptides (D_1 D_2) are enzymatically cleaved but are attached by weak non-covalent bonds to D_3

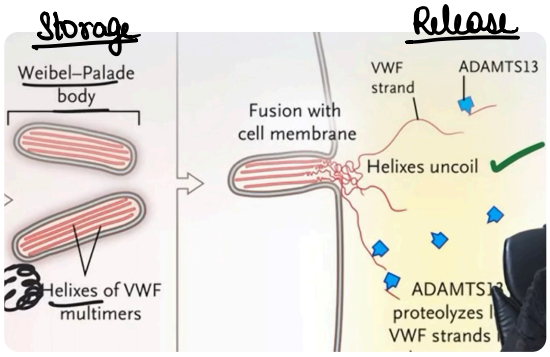
→ This happens in Golgi Apparatus.



④ Storage & Release:

→ Stored in Weibel-Palade Bodies in endothelial cells. Stored as coiled helices.

→ At the time of release, these WP bodies fuse c̄ the membrane, VWF uncoils & it is made to short strands by ADAMTS13 & then released



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→ When coiled, vWF is inactive, & is active when uncoiled

→ Deficiency of ADAMTS 13 ⟹ l/t Thrombotic Thrombocytopenic Purpura (TTP)

OVERVIEW OF VWD :

I. can be caused d/t null mutation that l/t ↓ synthesis of vWF monomer

Types : ① Type 1 (m/c) – 85% → Quantitative defect ⇒ ↓ Synthesis → not complete loss

② Type 2 → Qualitative defect (10 – 15%)

a) 2A → ↓ adhesion + ↓ multimers

b) 2B → ↑ adhesion + ↓ multimers

c) 2M → ↓ adhesion + (N) multimers

d) 2N → absent F VIII binding (Normandy – N)

③ Type 3 → Quantitative defect ⇒ Complete loss (<5%)

II. Mutation in A domain :

- Gain of function mutation → ↑ affinity to GpIb (Type 2B)
- Loss of function mutation → ↓ affinity to GpIb (Type 2M)

FUNCTIONS OF VWF :

① Platelet adhesions ⟷ GpIb
② F VIII carrier (↑ t½ of F VIII)
} main functions

③ Platelet aggregation

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AQUIRED VWD :

Causes – ① Malignancy [lymphoproliferative]
② MPN (more platelets are formed → more binding to Plt. ↓ more sequestration ↓ less VWF
③ Autoimmune disorders
④ Hypothyroidism
⑤ Drugs
⑥ Heyde's Syndrome (Severe Aortic Stenosis)
[AV malformations may be there in Colon l/t lower GI bleed]
⑦ LVAD (mechanical devices)

C/F OF VWD :

① VWD is a bleeding disorder
② Skin cuts/ abrasions ⟹ bleeding
③ Excessive bleeding after Tonsillectomy / after Tooth extraction
④ ♀ – ↑↑ severity
⑤ Hemophilia like picture is seen in Type 3/2N

TYPES OF VWD: (Next page ..... ☺ ⟹ Look there !)

* RIPA → Ristocetin induced Platelet Aggregation
VWF : RCo → Ratio of VWF & Ristocetin Cofactor
– tells about activity of VWF (in circulation)
VWF : Ag → VWF & Ag Ratio
– tells about circulating levels of VWF

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	Type	Defect	Bleeding	Mutations	RIPA	VWF: RCo	VWF: Ag	F VIII	VWF: RCo/ VWF: Ag	Multi-mers	Comments
①	Type 1 (AD)	Partial (Quantitative loss)	None to Mild	Null / Missense (↓ release)	↓	↓ (<30)	↓ (<30)	Ⓝ/↓	>0.6	Ⓝ Pattern	VWF ProPeptide ≥5 IU/dl
②	Type 2A → (AD>AR)	Qualitative def. [↓ adhesion + ↓ multimers]	Mod. to severe	Missense (except A_1/D_3 domains)	↓	↓ (<30)	↓ (<30)	Ⓝ/↓	<0.6	Absent	—
③	Type 2B → (AD>AR)	Qualitative def [↑ adhesion + ↓ multimers]	Mod. to severe	Missense of A_1 (gain of function)	↑ (Pseudo VWD)	↓ (<30)	↓ (<30)	Ⓝ/↓	<0.6	Absent	Thrombocytopenia seen
④	Type 2M → (AD>AR)	Qualitative def. + ↓ adhesion + Ⓝ multimers	Mod. to severe	Missense of A_1 (loss of function)	↓	↓ (<30)	↓ (<30)	Ⓝ/↓	<0.6	Ⓝ Pattern	—
⑤	Type 2N → (AD>AR)	Qualitative def. No binding $\bar{c}$ F VIII	Mod. to severe	Missense of D_3	↓	Ⓝ	Ⓝ	↓↓↓ (↓ F VIII ½ life & carrying)	>0.6	Ⓝ pattern	Clinically resembles Hemophilia
⑥	Type 3 → (AR)	Severe Quantitative defect. (Complete loss)	Severe	Null mutation	↓	↓↓↓ (<3)	↓↓↓ (<3)	↓↓↓ (↓ F VIII ½ life & carrying)	no comparision (non-measurable)	Absent	VWF PP <5 IU/dl (resembles Hemophilia)

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ALGORITHM:

Suspected VWD

[Bleeding disorder / (N) Platelets / (N) PT/INR / (N)/↓ F VIII & (N)/↑ aPTT / ab(n) PFA-100]

↓

VWF : RCo
VWF : Ag

- (N) → F VIII levels
  - (N) → Other bleeding/coagulation disorders
  - ↓ VWF – F VIII binding assay
    - (N) → Hemophilia
    - ab(n) → Type 2N VWD [VWF : RCo / VWF : Ag > 0.6]
- → Quantity
  - < 3 → Type 3
  - < 30 → Multimers?
    - (N) pattern → Type 1 (vs) 2M
      - VWF : RCo / VWF : Ag
        - > 0.6 → Type 1
        - < 0.6 → Type 2M
    - Absent → Type 2A (vs) 2B
      - RIPA
        - ↑ → Type 2B
        - ↓ → Type 2A

Difference b/w Type 3 & Type 1 (Severe):

Type 3	Severe Type 1
Multimers – absent	Multimers – (N) pattern
VWF PP < 5 IU/dl	VWF PP > 5 IU/dl

Rx OF VWD:

① Type 1 → DDAVP (Desmopressin) → augments the release of VWF
can also be used in Type 2/3

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② Type 2/3 → VWF replacement → Cryoprecipitate
F VIII concentrate
r-VWF (recombinant)

→ Tranexamic acid (can be used as adjunct)

Hemophilia	VWD
→ X-linked Recessive	→ AD (>AR)
→ ♂	→ ♂ = ♀ (♀ - ↑↑ severity)
→ Coagulative disorder	→ Bleeding disorder
→ Platelets - Ⓝ	→ Platelets - Ⓝ/↓
→ PFA-100 - Ⓝ	→ PFA-100 - abⓃ (except in 2N)
→ F VIII - ↓↓	→ F VIII - Ⓝ/↓ [↓↓ in 2N/3]
→ apTT - ↑↑	→ apTT - Ⓝ/↑ [↑↑ in 2N/3]
→ RIPA - Ⓝ	→ RIPA - ↓ (except 2B - ↑)
→ VWF - Ⓝ	→ VWF - ↓↓ (except 2N - Ⓝ)

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